APPLICATION NUMBER:

761066Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
PIND 113462

MEETING PRELIMINARY COMMENTS

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

Attention:  Kelly T. Boyle
CFO, Biologics Consulting Group, Inc.

Dear Ms. Boyle:

Please refer to your Pre-Investigational New Drug Application (PIND) file for SB4.

We also refer to your March 4, 2016, correspondence requesting a meeting to discuss the format and content of the BLA submission for SB4, proposed biosimilar to Enbrel (etanercept).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting.  The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, MS, RPh
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments
Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 26, 2016, between Samsung and the Division of Pulmonary, Allergy, and Rheumatology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND:
Samsung is developing SB4, a proposed biosimilar to US-licensed Enbrel (etanercept), approved in the U.S. for subcutaneous (SC) administration in treatment of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), plaque psoriasis (PsO), and juvenile idiopathic arthritis (JIA). The proposed biosimilar drug product is a single-use pre-filled syringe (PFS) containing 50 mg of SB4. A Type B meeting with the FDA was held February 22, 2012. The sponsor has continued to develop SB4 outside the U.S. and noted that SB4 has been approved for marketing by the Korean health authority in September 2015 and by the European Commission (EC) in January 2016.
QUESTIONS AND PRELIMINARY RESPONSES

Samsung’s questions from the briefing package are noted in italics font, and FDA’s responses are provided in normal font.

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

Question 1
During the Pre-Investigational New Drug Application Meeting with the FDA, ‘SAIT104’ was used as the laboratory code for SB4. After the corporate spin-off from Samsung Electronics Co., Ltd., the laboratory code was changed from SAIT104 to SB4. The laboratory code ‘SB4’ will be used throughout the CTD dossier, while it may still be referred to as SAIT104 in certain source documents. The previous laboratory code will be included in CTD Section 3.2.S.1.1 Nomenclature. Does the Agency agree or have any comments?

FDA response:
We agree with your proposal to use SB4 as a new laboratory code. It is also acceptable to use previous laboratory (SAIT10) and current CMO codes (BIIB602 or BIIB602-D) to refer to your proposed biosimilar product in the 351(k) application.

Question 2
In support of the 351(k) application, the Applicant has performed extensive quality similarity studies to demonstrate similarity between SB4 and US Enbrel®, in accordance with the FDA guidance ‘Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product’ and the advice received from the FDA pre-IND meeting held in 2012 (Annex 1). Does the Agency agree or have any comments?

FDA response:
The quality attributes listed in Table 3 in your meeting package generally appear reasonable for an assessment of analytical similarity of SB4 and US-licensed Enbrel and to establish an analytical bridge between SB4, US-licensed Enbrel, and EU-approved Enbrel. However, we have insufficient information to determine whether the test articles proposed for the analytical similarity studies are appropriate. Address the following in your 351(k) application:

a. You did not specify whether the analytical similarity assessment included SB4, US-licensed Enbrel, and EU-approved Enbrel lots used in the clinical studies. The analytical similarity studies should include SB4 product lots used in the clinical studies and proposed commercial product to establish a link between the quality attributes of the clinical lots and proposed commercial SB4 product. If the clinical and proposed commercial SB4 lots were manufactured by different processes, comparability between clinical and commercial SB4 lots should be demonstrated. The adequacy of these results is a review issue.

b. You propose to conduct structure-activity relationship (SAR) studies on HI-HPLC, charge and glycostructure variants in SB4 and EU-approved Enbrel. Your proposal would be acceptable, provided you submit data demonstrating that the species identified in SB4 and EU-approved Enbrel are the same or are relevant to US-licensed Enbrel. These data
include characterization of the product-related species in SB4, US-licensed Enbrel, and EU-approved Enbrel monitored by the HI-HPLC, charge and glycostructure methods.

c. You propose to conduct comparative photostability studies on SB4 and EU-approved Enbrel. You should include US-licensed Enbrel in this evaluation to support that SB4 is highly similar to the reference product.

d. You provided information on the implementation of the recommendations provided by the Agency in the meeting held on February 22, 2012. With respect to the implementations related to the comparator products, you state that you will clearly identify the source of the products used in the analytical studies. In your comments, you refer to a product identified as “KR Enbrel”, which we interpret is an etanercept product approved in Korea. Clarify the relevance of the data from analysis of “KR Enbrel” to a demonstration that SB4 is highly similar to the reference product, US-licensed Enbrel, and to the analytical bridge.

e. In your criticality risk ranking assessment (Table 58), you state that peak 3 by HIC was identified as a HMW species and the levels of this peak may affect potency and immunogenicity. Publicly available information indicates that analysis of Enbrel by HIC result in three peaks, with the third peak identified as a misfolded form of etanercept along with HMW and other species (US Patent 7294481). This misfolded form involves S-S pairing and demonstrated greatly reduced activity (Goswami, S. et al. Antibodies, 2013, 2, 452-500). As part of the evaluation of potency and the levels of the peak 3 by HIC in the similarity assessment, we recommend that you characterize the species corresponding to peak 3 (and other HIC peaks, if relevant) and evaluate whether these species may convert back to the correctly folded species under biological conditions. We recommend that you identify an appropriate model that represents in vivo biological conditions to conduct these evaluations (e.g. Jiang et al, 2013 Anal Biochem. 432:142; Wang et al, 2015 J Pharm and Biomed Anal. 102:519; and Min et al. 2015 Process Biochem. 30:1313).

f. We recommend that you consider evaluation of protein higher order structure (HOS) in US-licensed Enbrel using the proposed H/DX-MS method. Currently, you propose to use H/DX-MS to evaluate HOS of SB4 and EU-approved Enbrel. Although you propose to evaluate the three products using other orthogonal methods (e.g., SV-AUC, SEC-MALS, intrinsic and extrinsic fluorescence, DSC, DLS and FT-IR), these methods are generally not suitable to identify the location of protein conformation differences, if present. Therefore, you should consider evaluation of US-licensed Enbrel using H/DX-MS or other appropriate method to further support highly similar HOS between SB4 and the reference product, US-licensed Enbrel.

g. Refer to FDA response to question 3 regarding the number of SB4 lots proposed for the analytical similarity assessment.

Whether the data generated from your analysis of SB4, US-licensed Enbrel, and EU-approved Enbrel are sufficient to demonstrate that SB4 is highly similar to the reference product and to support establishing the analytical portion of the scientific bridge between the three products will be a review issue.

Question 3
The Applicant has performed extensive quality similarity studies in terms of structural characteristics (primary, high order and glycosylation), physicochemical properties (charge heterogeneity, purity and impurity) and biological activities (MoA-related functions and Fc-related functions). Based on a tiered
system (Tier 1, 2, and 3) in which approaches of varying statistical rigor were used, each attribute was assessed in a three-way bridge approach to demonstrate similarity between SB4 and US Enbrel® and to demonstrate comparability between EU and US Enbrel®. The Applicant believes that the proposed strategy of quality similarity assessment is sufficient to demonstrate similarity in quality between SB4 and US Enbrel® and to establish a quality bridge between EU and US Enbrel®, in support of a 351(k) application. Does the Agency agree or have any comments?

FDA response:
We do not agree that the analytical similarity strategy described in your meeting package is sufficient to demonstrate that SB4 is highly similar to the reference product and to establish an analytical bridge between SB4, US-licensed Enbrel and EU-approved Enbrel. Review your analytical similarity strategy to address the following:

a. The number of SB4 lots proposed for assessment of quality attributes in the three statistical tiers, outlined in Figure 1 on page 26 of your meeting package, is limited and may be insufficient for statistical evaluation of Tier 1 and Tier 2 attributes. We recommend that you analyze additional SB4 lots to conduct a meaningful evaluation of the analytical similarity between SB4 and the reference product and to establish a robust analytical bridge. Refer to comment (a) of FDA response to Question 2 and to comment (c) of this response, below.

b. You conducted a criticality risk assessment to support placement of quality attributes (QA) into statistical tiers using risk priority number (RPN) based on impact and uncertainty scores. QAs with RPN of >59 were assigned to Tier 1, QAs of 24 < RPN ≤ 59 were assigned to Tier 2 and QAs with RPN ≤ 24 were assigned to Tier 3.

Be aware that in addition to risk ranking, other factors should be considered in assigning QAs and assays to a particular tier. These factors include, for example, the levels of an attribute in both the reference product (as determined by your testing) and proposed biosimilar product, the sensitivity of an assay to detect differences between products, if any, and an understanding of the limitations in the type of statistical analysis that can be performed due to the nature of a quality attribute (e.g., whether the results from analysis of a QA is a numerical or qualitative read out). Based on these considerations, a quality attribute may be assigned to a tier different from that assigned based on risk ranking only.

In general, we expect selected very high risk quantitative QAs associated with the MOA of the product be analyzed by equivalence testing (Tier 1). QAs that are of high or moderate risk and result in numerical read out should be analyzed by quality ranges (Tier 2). QAs assigned to Tier 3 correspond to those of lowest risk (quantitative or qualitative readout) or are of higher risk but not amenable to formal tests of hypotheses or quantitative evaluation. Various forms of visual displays may be used to compare the distribution of values from the biosimilar and reference lots, and subjective determination of the similarity is made based on those displays.

Based on the approach described above, we find the placement of the attributes currently assigned to Tier 1 (TNFα neutralization by NF-kB reporter gene and TNFα binding) appropriate, however some of the Tier 3 attributes are not appropriately assigned (e.g., chemical modifications, carbohydrate analysis, FcγRIIa and FcγRIIIa binding and CDC). Revise your QA tier attribute assignment to address these concerns.
c. In your proposed Tier 1 equivalence test, you have four SB4 drug product batches. The number of proposed biosimilar product lots is not sufficient to obtain stable estimates of the mean and the variability of the biosimilar product. In addition, you have 32 and 34 batches of US-licensed Enbrel and EU-approved Enbrel for TNF-α binding, and 28 and 24 batches of US-licensed Enbrel and EU-approved Enbrel for TNF-α neutralization, respectively. Since the number of reference and comparator product lots is much larger than the number of proposed biosimilar lots, the information from the comparator products may dominate the Tier 1 equivalence test. Hence, we recommend that you increase the number of SB4 drug product batches.

All reference product lots can be used to compute the confidence interval and to estimate the equivalence margin. In general, we recommend using a similar number of lots of the proposed biosimilar and the reference product. When the number of reference product lots is much larger than the number of proposed biosimilar lots (e.g., more than 50 %), we recommend the following equation for sample size imbalance adjustment to calculate the confidence interval of the mean difference:

\[
\left( \bar{X}_B - \bar{X}_R \right) \pm t_{1-\alpha, df^*} \times \sqrt{\frac{S_B^2}{n_B} + \frac{S_R^2}{n_R^*}}
\]

where \( n_R^* = \min(1.5 \times n_B, n_R) \), \( n_B \) and \( n_R \) are respectively the number of the proposed biosimilar lots and the number of the reference product lots; \( \bar{X}_B \) and \( \bar{X}_R \) are respectively the sample mean of the proposed biosimilar lots and the sample mean of the reference product lots; \( S_B^2 \) and \( S_R^2 \) are respectively the sample variance estimated by all the biosimilar lots and the sample variance estimated by all the reference lots; \( t_{1-\alpha, df^*} \) is the \( 1-\alpha \) quantile of the \( t \)-distribution with degrees of freedom \( df^* \) where \( df^* \) can be approximated by the Satterthwaite method:

\[
df = \frac{\left( \frac{S_B^2}{n_B^*} + \frac{S_R^2}{n_R} \right)^2}{\frac{s_B^4}{n_B^* (n_B^* - 1)} + \frac{s_R^4}{n_R (n_R - 1)}}.
\]

**Question 4**
The Applicant has established release and stability specifications for SB4 DS and DP to ensure product quality, based on the product risk assessment and the advice received from the FDA pre-IND meeting held in 2012 (Annex 1), and considers sufficient to be included in the 351(k) application for the Agency’s review. Does the Agency agree or have any comments?

**FDA response:**
The approach used to establish release and stability drug substance (DS) and drug product (DP) specifications described in your meeting package appears generally reasonable. However, in addition to the factors outlined in your submission, such as clinical process batch data, and process capability and variability, you should consider the assessed range of the quality
attributes of the reference product when setting the specifications acceptance criteria for critical quality attributes of your product (e.g. potency).

With respect to our recommendation to include a specification for charge variants provided in a Type B meeting held on February 22, 2012, you state that charge variant specifications are not proposed based on SAR studies performed for charge variants and the lack of a significant trend with regards to % acidic and %basic variants evaluated during long-term stability studies of SB4. The adequacy of your justification for the release and stability specifications of your product, including the charge variants specification will be a review issue.

Finally, we note that you proposed to include container closer integrity and sterility testing in the DP shelf-life specification. For the shelf-life specifications of DP, container closer integrity testing may be conducted in lieu of sterility testing. Refer to FDA Guidance for Industry Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products.

**Question 5**
The Applicant proposes to claim expiry dating of SB4 DS and DP at the time of licensure, based on stability data of PVR batches and the comparability between clinical and PVR batches. Does the Agency agree or have any comments?

**FDA response:**
You propose to provide in your 351 (k) application 24 months and 18 months of real-time stability data for three process validation batches of DS and DP, respectively and 36 months of real-time stability data for clinical DS (1 batch) and DP (three batches) batches to support shelf life of your product. Your proposal is acceptable provided you submit data to demonstrate comparability between process validation and clinical batches and the products were stored in a container closure system which properly represent the final commercial container closure system, and the product was stored under the same storage conditions. The actual shelf-life of your product will be determined at the time of licensure. Be aware that you may provide updated stability data during review of your 351 (k) application, however, the last stability data update should be provided no later than 4 months prior to the BsUFA action date.

**Question 6**
After BLA approval, expiry dating of the SB4 DS and DP will be extended based upon full shelf life data on commercial scale batches obtained from protocols approved in the 351(k) application, and will be documented in the annual report, in accordance with 21 CFR 601.12 (d) (iii). The stability protocols will be presented in the CTD according to the plan below. Does the Agency agree or have any comments?

**FDA response:**
You propose to extend expiry dating of the SB4 DS and DP based on an approved stability protocol and the long-term stability data of three clinical DS/DP lots, but limited to the last acceptable stability time point available for PVR DS/DP batches plus six months. Your proposal is acceptable. Also refer to FDA response to Question 5.
**Question 7**

The human factor studies for SB4 Pre-filled Syringe (PFS) consists of 3 formative evaluation studies performed to identify potential use errors that may result in harm to the user, and 1 summative validation study performed to demonstrate that the PFS can be used by the intended users without serious use errors or problems. The Applicant considers these studies have sufficiently fulfilled the requirements for human factor studies to be included in the 351(k) application, and considers that no additional human factor study will be required for the Agency’s review. Does the Agency agree or have any comments?

**FDA response:**

The adequacy of the Human Factors (HF) results is a review issue. However, we note that you have performed some of the HF studies outside the USA. The HF summative study should utilize the intended-to-be-marketed presentation and materials (i.e., Instructions for Use, carton, packaging) and the study participants must be representative of the USA population. Differences in literacy levels, language, idioms, etc. between the USA and foreign countries might bias study results and not be representative of users in the USA.

You indicated that your proposed PFS exactly follows the same configuration to that of the reference product (i.e., US-licensed Enbrel). Therefore, you should first perform a comprehensive use-related risk analysis. If this analysis does not identify any unique risks with your proposed PFS when compared to the reference product, it is likely that no human factors studies will be needed, and we recommend that you submit this analysis to FDA for review and concurrence.

Otherwise, if you have determined that an HF validation study is needed, then note that our expectations for products to be marketed in the US, the HF validation study should include US residents, and utilize the final finished presentation, labeling including Instructions for Use, carton, and packaging that represent the commercial product.

**Question 8**

The Applicant has conducted in vivo and in vitro non-clinical studies in accordance with ‘Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product’. The studies include an efficacy study in BALB/c mice and a PK study in SD rats to demonstrate similarity between SB4 and Enbrel®. In addition, the Applicant performed a 4-week comparative toxicology study in EU Enbrel® under Good Laboratory Practice (GLP) conditions according to the FDA’s recommendation from the FDA pre-IND meeting held in 2012 (Annex 1). The Applicant believes that the non-clinical studies conducted are adequate and sufficient for a 351(k) application. Does the Agency agree or have any comments?

**FDA response:**

We agree that the in vivo nonclinical studies (i.e., an efficacy study in BALB/c mice, a PK study in SD rats, and a 4-week comparative toxicology study in monkeys) are sufficient for a 351(k) application.

**Question 9**

The Applicant has conducted one clinical Phase I study and one clinical Phase III study to demonstrate clinical similarity between SB4 and Enbrel®. Furthermore, an additional 52-week open-label extension period was included to further demonstrate the similarity of the SB4 maintenance
group (SB4/SB4) and the SB4 treatment group that transitioned from Enbrel® (Enbrel®/SB4) in respect to efficacy, safety and immunogenicity. The complete data package of the clinical Phase I and the clinical Phase III (including the 52-week extension period) studies will be included in the 351(k) application. Does the Agency agree or have any comments?

**FDA response:**

Your proposal to submit a data package consisting of the clinical PK similarity study SB4-G11-NHV and the comparative clinical study SB4-G31-RA in rheumatoid arthritis, including the 52-week extension period, is reasonable. In the extension study, patients who were originally randomized to SB4 continued on treatment with SB4, while those originally randomized to EU-approved Enbrel underwent a single transition to SB4. This approach does not compare patients who underwent a single transition from EU-approved Enbrel to SB4 with patients continuing on EU-approved Enbrel, which is the comparison of interest. This approach also may be confounded by differences in completer subsets and residual differences due to different double-blind treatments. Therefore, we also request that you provide a comparison of the baseline characteristics at the start of the extension study of the patients undergoing a single transition and those who continue on SB4. In addition, provide a comparison of the safety and immunogenicity rates in the patients before and after the single transition. Whether the proposed data package will be sufficient to support a demonstration of no clinically meaningful differences of SB4 to US-licensed Enbrel will be a review issue.

The immunogenicity data shows differences in the incidence of ADA formation between the groups treated with SB4 as compared to the groups treated with EU-approved Enbrel in both clinical studies SB4-G11-NHV and SB4-G31-RA. In your BLA submission, provide your assessment on factors that may contribute to the observed differences, including the immunogenicity assay. Also, provide a justification as to why these results do not preclude a demonstration of no clinically meaningful differences.

**Question 10**

The Applicant analyzed the primary endpoint of ACR20 at Week 24 with non-parametric method using SAS Macro NParCov version 2.0 as the primary analysis and the time-response modeling from baseline to Week 24 as a supportive analysis. The Applicant considers that the analysis plan applied was appropriate to demonstrate similarity in efficacy profiles between SB4 and Enbrel®. Does the Agency agree or have any comments?

**FDA response:**

The statistical methods employed in the primary and supportive analyses of ACR20 at Week 24 are generally reasonable. However, we have the following additional statistical comments:

- Your primary analysis for Study SB4-G31-RA was carried out in a per-protocol population using a 95% confidence interval and a similarity margin of ±15%. We currently recommend that the primary analysis be carried out in all randomized patients, and that 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% (see rationale for this margin below). You should justify in your application that the primary results meet these criteria.
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.

To assess the robustness of the primary analysis results with regards to missing data, we recommend that you conduct 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 SB4 arm had dissimilar outcomes than dropouts on the EU-approved Enbrel 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. Then, the plausibility of those assumptions can be discussed.

**Similarity Margin Justification**

We currently recommend that the similarity margin for your proposed comparative clinical study (CCS) in rheumatoid arthritis be no greater in magnitude than ±12%. The recommended margin of ±12% is based on considerations aimed at weighing the clinical importance of various differences in effect against the feasibility of different study sizes. 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 45–55% of conservative estimates of treatment effect sizes relative to placebo for Enbrel. 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 ±12% similarity margin with 80–90% power under equality likely requires 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 you provide adequate justification for such an approach and for the margin chosen.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Week</th>
<th>MTX + Placebo</th>
<th>MTX + Enbrel</th>
<th>Difference in % Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>% Response</td>
<td>N</td>
</tr>
<tr>
<td>Weinblatt et al.¹</td>
<td>12</td>
<td>30</td>
<td>33%</td>
<td>59</td>
</tr>
<tr>
<td>Lan et al.²</td>
<td>12</td>
<td>29</td>
<td>34%</td>
<td>29</td>
</tr>
<tr>
<td>Meta-Analysis (fixed effects³): Difference (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3936504
Reference ID: 4424577
Meta-Analysis (random effects⁴): Difference (95% CI)  
<table>
<thead>
<tr>
<th></th>
<th>44.0% (21.8%, 66.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogeneity p-value</td>
<td>0.13</td>
</tr>
</tbody>
</table>


3 Based on Mantel-Haenszel weights

4 Based on DerSimonian-Laird approach

**Question 11**

**A. Due to the proposed pharmaceutical form, 50 mg/mL,**  

*Does the Agency agree or have any comments?*

**FDA response:**

We do not agree. You stated that you intend to seek licensure of your proposed biosimilar to US-licensed Enbrel only for treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. Your proposal would not comply with requirements under the Pediatric Research Equity Act (PREA), and thus would not be acceptable (see section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)). Under PREA, 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.

Because you intend to seek licensure of your proposed biosimilar product for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis, 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.
C. The Applicant plans to incorporate data and information from the reference product labeling, with appropriate SB4 product-specific modifications as an initial labeling draft in the 351(k) application. Does the Agency agree or have any comments?

FDA response:
It would be reasonable to incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications, as a starting point. Submit your draft proposed labeling for SB4 in Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) format. We recommend that you refer to the Draft Guidance: Labeling for Biosimilar Products Guidance for Industry (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf). We request that your annotated labeling identify, with adequate specificity, the source of all data and information presented. We will provide additional comments on draft proposed labeling during review of your BLA.

Question 12 - Extrapolation
Similarity of SB4 and Enbrel® has been demonstrated in a comprehensive similarity exercise, including extensive quality comparisons, a series of non-clinical studies, a Phase I study in healthy male subjects, and a Phase III study in RA subjects (including supportive PK assessments). The results of this similarity exercise demonstrated a high degree of similarity between SB4 and Enbrel®. The Applicant intends to claim all other indications of the reference medicinal product [redacted] based on extrapolation. The Applicant intends to submit the scientific justification of extrapolation of indications based on a review of published data demonstrating the shared mechanism of action across all authorized indications and a discussion of data included in the 351(k) application to support the validity of extrapolation. Does the Agency agree or have any comments?

FDA response:
If SB4 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 clinical
study(ies) sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, you may seek licensure of SB4 for one or more additional conditions of use for which US-licensed Enbrel is licensed. However, 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.

Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action in each condition of use for 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/receptor(s);
  - The relationships between product structure and target/receptor interactions;
  - The location and expression of the target/receptor(s).
- The PK and biodistribution of the product in different patient populations (relevant PD measures also may provide important information on the mechanism of action);
- The immunogenicity 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); and
- 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 etanercept and these additional factors for extrapolating clinical data from one condition of use to other conditions of use being sought will be a review issue.

**Question 13**

The clinical study program of SB4 consists of two studies, a Phase I study in healthy male volunteers and a Phase III study in RA patients. Due to the differences between the studies (i.e. study populations, objectives, treatment regimen), generating an Integrated Summaries of Effectiveness (ISE) and Integrated Summaries of Safety (ISS) by combining these two study results is deemed inappropriate. Thus, the Applicant intends to repeat the contents of Module 2 (Section 2.7.3 and 2.7.4) as the ISS/ISE in Module 5 (Section 5.3.5.3). Does the Agency agree or have any comments?

**FDA response:**

Your proposal is reasonable.

**Question 14**

The Applicant does not intend to submit a proposed REMS for SB4 as part of the 351(k) application, considering that not only no new safety concern comparing with the reference product was detected during the clinical studies of SB4, but also the reference product has been released from REMS requirement. Accordingly, the Applicant intends to develop a Medication Guide for patient which is not part of REMS. Does the Agency agree or have any comments?
FDA response:
In August 2011, FDA released US-licensed Enbrel from its previously approved REMS and determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21CFR208.1. Accordingly, at this time, we agree that developing a Medication Guide for patients, outside of a REMS, would be appropriate for your proposed biosimilar product. However, we have insufficient information to conclusively determine whether a REMS will be necessary to ensure that the benefits of SB4 outweigh the risks. Based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

Question 15

FDA response:
We do not agree. As discussed in Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf, FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed PSP prior to the submission of your planned 351(k) BLA. Sections 505B(e)(2)(C) and 505B(e)(3) set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA cannot commit to spending less than 90 days to provide initial comments on your iPSP, or less than 30 days to confirm agreement with your agreed iPSP. It should be noted that you may opt to spend less than 90 days for review of our comments on your iPSP and submission of your agreed iPSP. You should submit an agreed and confirmed pediatric study plan with your BLA submission. However, at this time, the lack of an agreed PSP for this proposed 351(k) BLA would not, on its own, preclude filing of an otherwise acceptable 351(k) BLA submission.

Question 16

The Applicant plans to compose an eCTD dossier as the core structure based on the Agency’s opinion on the following questions.

a) The Applicant plans to include a justification of extrapolation (for indications) mainly under Section 2.5.4 based on the perspective of MoA, PK profile, efficacy and safety and immunogenicity of each approved indication of Enbrel®. Does the Agency agree or have any comments?

FDA response:
See FDA response to Question 12 regarding the expected information to include in a justification of extrapolation. Your proposal to include this information under Section 2.5.4 is reasonable.
b) The Applicant plans to include in 5.3.7 Case Report Forms due to AEs in the eCTD at the time of 351(k) application.

FDA response:
We do not agree. You should include case report forms and narratives for subjects and patients for deaths and for SAEs, adverse events of special interest, and adverse events leading to premature discontinuation.

FDA Additional Comments:

A. Product Quality Microbiology

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(k) BLA submission.

I. All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Manufacturing facility information should be included in the 351(k) BLA (3.2.A) as background information for the pre-license inspections. Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

II. The CMC Drug Substance section of the 351(k) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The provided information should include, but not be limited to the following:

a. Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).

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

c. Data demonstrating microbial control (3.2.S.2.5).

d. Bioburden and endotoxin data obtained during manufacture of at least three process qualification lots (3.2.S.2.5).

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

f. Drug substance bioburden and endotoxin release specifications (3.2.S.4).
g. Summary report and results from bioburden and endotoxin test methods qualification performed for in-process intermediates and the drug substance should be provided (3.2.S.4). In addition, the test methods should be described.

III. The CMC Drug Product section of the 351(k) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry “Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products” http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

a. Provide the following information in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:
   - Description of the manufacturing areas and fill line, including air classifications.
   - Description of the environmental and personnel monitoring programs.
   - Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.
   - Description of the sterilizing filter (supplier, membrane material, membrane surface area, etc.), and the acceptance criterion for post-use integrity testing.
   - Parameters for filling and stoppering.
   - Processing and hold time limits, including the time limit for sterilizing filtration.

b. Provide information and validation data summaries in Section 3.2.P.3.5 for the following:
   - Bacterial filter retention study for the sterilizing filter.
   - Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program. For information located in Drug Master Files (DMFs), provide Letters of Authorization which list the relevant depyrogenation and sterilization sites and which clearly identify the location of the relevant information within the DMF.
   - Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
   - Isolator decontamination, if applicable.
   - Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.
   - Shipping validation studies. The effects of varying air pressure on pre-filled syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data that demonstrate that the pre-filled syringe plunger movement during air transportation does not impact product sterility.

c. Provide the following information regarding drug product testing:
Qualification of the bioburden, sterility and endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate. In addition, the test methods should be described.

Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).

Low endotoxin recovery studies. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin standard (CSE or RSE) into undiluted drug product and testing for recoverable endotoxin over time.

Container closure integrity testing information and data. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) and at expiry (3.2.P.8.2).

B. Device

You have provided minimal information regarding the design of the device constituent parts of the proposed pre-filled syringe combination products. Within future investigational or marketing applications, we expect that you will provide all necessary information to support the safety and functionality of the constituent parts. This information includes the following:

- A description of the complete system, including individual device components or configurations.
- A complete description of design control inputs, in the form of device requirements and specifications, which fully describe the attributes of the system and their acceptability in the context of the intended use of the system and the medication being delivered.
- Design output information in the form of test reports and other activities which verify the individual requirements and specifications for the system and validate the system is fit for its intended use within the context of the medication being delivered.
- Risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable misuse, and potential system failure states. Such an analysis should clearly describe system hazards, mitigations implemented to reduce the risk of those hazards, effectiveness of the mitigation, as well as conclusions of the acceptability of system risks within the final finished system.

All verification and validation data should be performed on the final finished sterilized combination product. You are advised to consult the following guidance documents and consensus standards prior to future investigational or marketing applications:

- Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4
  http://www.fda.gov/RegulatoryInformation/Guidances/ucm346727.htm
- ISO 11040-4 Prefilled Syringes-Part 4: Glass barrels for injectables.
- ISO 11040-5 Prefilled Syringes-Part 5: Plunger stoppers for injectables.

If the device will consist of a Sharps Injury prevention feature:

- Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features.
  


C. Facilities

From a facilities perspective, all facilities for SB4 manufacture should be in a state of compliance and inspection ready. For the Drug Substance facility, we expect that the facility is manufacturing SB4 during inspection.

D. Nonclinical

A safety assessment of extractables and leachables with the pre-filled syringe (PFS) should be available with the BLA.

E. Clinical

To define anaphylactic reactions in a more consistent and less subjective manner you should define and assess any potential cases of anaphylaxis using the criteria discussed in the statement paper from the Second Symposium on the Definition and Management of Anaphylaxis (Sampson HA et al., J Allergy Clin Immunol. 2006 Feb;117(2):391-7). If not prospectively captured, we request that you retrospectively identify cases using these NIAID/FAAN criteria.

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 PLLR 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.

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

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.
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.”

<table>
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<th>DSI Pre-NDA Request Item</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
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<td>I</td>
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<td>Data listings, by study</td>
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<tr>
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<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
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<tr>
<td>II</td>
<td>data-listing-dataset</td>
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<tr>
<td></td>
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<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
[drive] [m5]
  └── datasets
      └── bimo
          └── site-level
```

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.

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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

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

For general help with eCTD submissions: ESUB@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE H CHUNG
05/25/2016
Christine Ford (formerly Chung)