# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761054Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 113461

**MEETING MINUTES**

Samsung Bioepis Co., Ltd., a Samsung Company
c/o Quintiles, Inc.
4920 East Greensboro Chapel Hill Rd.
Graham, NC 27253

Attention: Kamali Chance, MPH, PhD, RAC
Vice President, Head, Global Biosimilars Regulatory Strategy

Dear Dr. Chance:

Please refer to your Pre-Investigational New Drug Application (PIND) file for SB2.

We also refer to the meeting between representatives of your firm and the FDA on December 14, 2015. The purpose of the meeting was to the formatting, content, and database format for the BLA.

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) 796-3420.

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:
Meeting Minutes

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | Biosimilar Product Development (BPD) |
| **Meeting Category:** | BPD Type 4 |
| **Meeting Date and Time:** | December 14, 2015 1:00 – 2:30 P.M. |
| **Meeting Location:** | White Oak Building 22, Conference Room: 1421 |
| **Application Number:** | PIND 113461 |
| **Product Name:** | SB2 |
| **Indication:** | SB2 is being developed for the same indications as approved for US-licensed Remicade |
| **Sponsor/Applicant Name:** | Samsung Bioepis Co., Ltd. (Samsung) |
| **Meeting Chair:** | Dr. Badrul Chowdhury, Director |
| **Meeting Recorder:** | Christine Ford, Regulatory Project Manager |

**FDA ATTENDEES:**

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, MD, Supervisory Associate Director, DPARP
Nikolay Nikolov, MD, Clinical Team Leader, DPARP
Keith Hull, MD, PhD, Clinical Reviewer, DPARP
Timothy Robison, PhD, Team Leader, Nonclinical, DPARP
Christine Ford, MS, RPh, Regulatory Project Manager, DPARP
David Frucht, MD, Director (Acting), Division of Biotechnology Review and Research II (DBRR II)
Kurt Brorson, PhD, Product Quality Team Leader, DBRR II
Cyrus Agarabi, PhD, Product Quality Reviewer, DBRR II
Yi Tsong, PhD, Director, Division of Biometrics VI (DBVI)
Meiyu Shen, PhD, Team Leader, DBVI
Sungwoo Choi, PhD, Biometrics Reviewer, DBVI
Gregory Levin, PhD, Team Leader, Division of Biometrics II (DBII)
Yongman Kim, PhD, Biometrics Reviewer, DBII
Ping Ji, PhD, Acting Team Leader, Division of Clinical Pharmacology II (DCPII)
Lei He, PhD, Clinical Pharmacology Reviewer, DCPII
Patrick Raulerson, JD, Senior Regulatory Counsel, Division of Regulatory Policy
Sue Lim, MD, Senior Staff Fellow, Therapeutic Biologics & Biosimilars Staff (TBBS)
Nicole Verdun, MD, Reviewer, TBBS
Neel Patel, PharmD, Regulatory Project Manager, TBBS

Jessica J. Lee, MD, Clinical Team Leader, Division of Gastroenterology and Inborn Errors Products (DGIEP) – joined by phone
Juli Tomaino, MD, Clinical Reviewer, DGIEP

**SPONSOR ATTENDEES:**

Hee Kyung Kim, BPH, MBA Vice President, Regulatory Affairs Team
Young-Phil Lee, Vice President, Quality Evaluation Team
Young Kook Kim, Vice President, Drug Product Team
Inyoung Baek, Director, Medical and Lifecycle Safety Team
Young Hee Rho, Director, Medical and Lifecycle Safety Team
Hyung Ki Park, Director, Regulatory Affairs Team
ByoungIn Jung, Senior Manager, Regulatory Affairs Team
In Hye Cho, M.Pharm, Assistant Manager, Regulatory Affairs Team

Kamali Chance, MPH, PhD, RAC, Qunitiles, Vice President, Head, Global Biosimilars Regulatory Strategy

*Joining by phone from Korea:*
Chul Kim, Vice President, Medical and Lifecycle Safety Team
Sean Paek, Vice President, Program Management Team
HongSeok Ji, Vice President, Process Innovation Team
Paul Song, Vice President, Cell Engineering Team
Donghoon Shin Director, Medical and Lifecycle Safety Team
Joowon Lee Director, Medical and Lifecycle Safety Team
Hyung Min Kim, Principal Engineer, Program Management Team
Won Young Yoo, Principal Engineer, Cell Line Development Group
Byung Soo Gim, Principal Engineer, Manufacturing Mgt. Group
Jae Sun Lee, Principal Engineer, Cell Culture Process Group
Yoon Seok Lee, Principal Engineer, Purification Process Group
Tae-Soo Lee, Principal Engineer, Device Group
Yeon Joo Hong, Senior Engineer, Bioassay Group 1
Kyungho Kim, Senior Manager, Regulatory Affairs Team
Hyun Lee, Senior Engineer, Regulatory Affairs Team
Yeosun Hong, Manager, Regulatory Affairs Team
Narae Bae, Manager, Regulatory Affairs Team
Euihan Jung, Manager, Regulatory Affairs Team
Garam Lee, Assistant Manager, Regulatory Affairs Team
Jeonghyun Choi, Engineer, Quality Innovation Team
Jong Min Park, Engineer, Analytical Method Development Group
Jessica Bae, Associate, Regulatory Affairs Team
Minkyu Choi, Associate, Regulatory Affairs Team

**Background:**

Samsung is developing SB2 as a proposed biosimilar to US-licensed Remicade (infliximab) and requested a meeting to discuss format, content and database structure for the BLA submission. The sponsor is planning to submit their 351(k) BLA in 2016. The electronic briefing package

was submitted with the meeting request, and was received September 16, 2015. The questions labeled below as "additional question" were submitted by email on November 18, 2015.

After review of the meeting package, FDA provided meeting preliminary comments to the sponsor's questions on December 11, 2015.

Samsung emailed their responses on the morning of the meeting, December 14, 2015, and specified areas that they would like to further discuss with FDA. Samsung's comments are incorporated into the body of the minutes as well as provided as an Appendix to the minutes.

The content of the letter is printed below, with the sponsor's questions from the briefing package in *italics;* FDA's responses (meeting preliminary comments) in normal font; and Samsung's emailed responses also noted in *italics*. Summary of meeting discussions, if any, are found in **bold normal font** following the specific area of discussion.

## QUESTIONS AND RESPONSES

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***

*The Applicant proposes to claim expiry dating of* (b) (4) *DP as 30 months (24 months stability data on PVR batches plus 6 months) at the time of licensure, based on stability data of PVR batches and the comparability between clinical and PVR batches. Does the Agency agree?*

FDA response:
This approach is acceptable.

***Question 2***

*The Applicant established release and stability specifications for SB2 DS and DP based on the product risk assessment and the previous discussion with the FDA at the Pre-IND meeting. Does the Agency have any further comments whether the established release and stability specifications are adequate and sufficient to be included in 351(k) application for the Agency's review?*

FDA response:
Your proposal for establishing the release and stability specifications of drug substance and drug product appears, in general, reasonable. However, since FcγRIIIA binding is an important product attribute, include an assay that measures binding avidity in your drug product release and stability strategy. Note that a final determination of the acceptability of your proposal will be made upon review of your 351 (k) application.

*Samsung's emailed response:*

- *The Applicant considers that the Agency recommended inclusion of the FcγRIIIa binding assay in the product release and stability specification because FcγRIIIa binding activity is known to be highly correlated with ADCC.*

**Discussion:**
**FDA confirmed the Applicant's understanding.**

(b) (4)

[redacted]

**Discussion:**
**Samsung proposed to use a test method for measuring %[afucose+HM] instead of the FcγRIIIa binding assay.**

**FDA replied this will be a review issue. As there is a possibility that other glycans not proposed for testing could impact FcγRIIIa binding, it is highly doubtful that Samsung's proposed approach will be adequate in the absence of ruling out**

**contributions from other glycans. For this reason, FDA continued to recommend the inclusion of the FcγRIIIa binding assay as part of the product release as a direct assessment of the binding affinity, which is an important product attribute.**

(b) (4)

**FDA responded that this testing point seemed reasonable, but asked that Samsung provide the justification for this approach in the BLA.**

***Question 3***

*The Applicant performed comparability assessment to demonstrate comparability between SB2 pilot, clinical and PVR batches in terms of structural, physicochemical, biophysical and biological characteristics. Does the Agency have any further comments whether the comparability assessment results are adequate and sufficient to be included in 351(k) application for the Agency's review?*

FDA response:
The overall comparability approach appears reasonable; however, a final determination of the acceptability of your proposal will be made upon review of your 351 (k) application. Additionally, provide justification for the discarded process validation batches and clarify whether there was a deviation or out of specification (OOS) investigation for batches HP5-14-603-001, -002, and -003.

*Samsung's emailed response:*

- (b) (4)
- *Detailed information will be included in the 351(k) application.*

**Discussion:**

**FDA noted that it is advisable to** (b) (4) **In particular, the sponsor should include internal testing upon receipt and quality release and not solely rely on vendor testing and specifications. The BLA should include the above referenced deviation report.**

***Question 4***

*As per the recommendation by the Agency, the Applicant employed the fixed SD approach for similarity assessment on tier 2 quality attributes. The fixed 3SD approach was taken for analyzing all tier 2 quality attributes, with the exception of %HMW to which 2.5SD was applied*

*due to its high data variability. Does the Agency have any further comments with respect to the tier 2 analysis and whether it is sufficient to be reviewed in 351(k) application?*

FDA response:
The overall approach described in table 91may be reasonable. However you should provide a justification for each selected multiplier on an assay-specific basis.

In addition we have the following concerns:

- Regarding table 91, justify use of (b) (4)

*Samsung's emailed response:*

– (b) (4)

–

**Discussion:**

**FDA responded that the quality range for comparison should be based on testing lots of the reference product alone,** (b) (4)

**Samsung stated that the quality range will be derived from the reference product.** (b) (4) .

(b) (4) **Furthermore, FDA noted that this new proposal for the SDM was emailed the morning of the meeting and is different from their original proposal in Table 92 submitted in the briefing package.**

**Samsung then proposed that a** (b) (4) .

**FDA recommended that Samsung choose one strategy and propose it for review.**

- Submit assay results from individual product lots, not aggregated and averaged for each assay. Submit these data in a tabular format, containing SB2, EU-approved infliximab and US-licensed reference product data side-by-side.
- For data derived from product quality assays dependent on protein concentration presented in this package, address whether the protein concentration in each test article was verified and corrected by an independent measurement post reconstitution (e.g., A280 measurement) prior to use in the assays.

  *Samsung's emailed response:*
  – *Prior to use in the assays, protein concentration in each test article was verified and corrected by A280 measurement post reconstitution.*

  **Discussion:**
  **FDA replied that this was acceptable.**

- In the analytical similarity exercise, the 8 current drug product lots used were manufactured from 5 drug substance lots. We do not consider different drug product batches produced from the same drug substance batches to be independent for this similarity exercise. Therefore, the current number of lots used provides insufficient power to analyze the data by Tier 1. We recommend you use an adequate number of independent biosimilar drug product lots to increase the statistical power of your Tier 1 analysis. Alternatively, for a more limited number of lots as you currently have, you may consider calculating the confidence interval with a lower confidence level to ensure adequate power. In this situation, the lower confidence level would be expected to be appropriately addressed by the final manufacturing control strategy.

  *Samsung's emailed response:*
  – (b) (4)
  –
  –
  –

  **Discussion:**
  **FDA responded that it is impossible for the Sponsor to know which Reference Product DS lots were used to manufacture the US-licensed Remicade DP lots that were used for the analytical similarity assessment. They should use Samsung DP lots sourced from independent DS lots because while some attributes such as aggregation may be affected by the drug product manufacturing process, other important attributes such as glycosylation and FcγRIIIa binding are not. Thus, only DP lots sourced from independent DS lots can truly capture the inherent variability of their product.**

**Samsung noted that the lots currently being used for the similarity assessment are (b) (4) liters, and a recommendation to produce additional lots would be burdensome. They asked if additional DS lots would be needed if lot-to-lot variability were low.**

**FDA stated that power for statistical analysis will be small with only 5 DS lots, and it would be better to have additional lots. Ultimately it is the sponsor's risk. From FDA's standpoint, DP lots manufactured from the same DS lot will be considered the same for statistical analysis purposes for the reason stated above. From this standpoint, how and which tests are used does not matter; the attribute results should be independent. If there are an inadequate number of DS lots, analytical properties cannot be properly assessed from a statistical standpoint.**

**Samsung asked whether additional DS lots could be manufactured at small scale if additional lots were necessary for testing.**

**FDA stated with justification this approach could be considered. The process needs to be an appropriately scaled down model of actual manufacturing and the small scale lots would require the demonstration of adequate comparability with the five previously manufactured lots used so far for the similarity assessment. It would be preferable that the degree of scale down be minimized (i.e., avoid lab scale).**

- FDA does not recommend splitting the reference product lots into two groups. Instead, FDA recommends using all reference lots for estimating variability in the calculation of margin and for calculating confidence intervals in equivalence testing. However, FDA recommends that the confidence interval should be changed to the following formula:

$$\overline{X}_B - \overline{X}_R \pm t_\alpha\left(n_B + \min\left(n_R, 1.5n_B\right) - 2\right) S\sqrt{1/n_B + 1/\min\left(n_R, 1.5n_B\right)}$$

Here $n_B$ and $n_R$ are respectively, the number of the proposed biosimilar lots and the number of US-licensed reference lots; $\overline{X}_B$ and $\overline{X}_R$ are respectively, the sample mean of the proposed biosimilar lots and the sample mean of US-licensed reference product lots; $S$ is the pooled sample standard deviation of the proposed biosimilar lots and US-licensed reference product lots; and $t_\alpha\left(n_B + \min\left(n_R, 1.5n_B\right) - 2\right)$ is 1-$\alpha$ quantile of $t$-distribution with degrees of freedom $n_B + \min\left(n_R, 1.5n_B\right) - 2$.

*Samsung's emailed response:*

- *We agree.*
- *Please clarify whether the following formula is appropriate for calculation of the pooled sample standard deviation (SD).*

(b) (4)

**Discussion:**

**FDA stated that equal variance should not be assumed. They recommended that the sponsor estimate variance for the proposed biosimilar product and reference product separately. FDA noted that the updated formula will be provided as a post-meeting note.**

**FDA Post-meeting comments:**

**FDA had previously recommended in the meeting minutes dated August 18, 2015 that it is preferable to have equal numbers of lots of the proposed biosimilar product and the reference product for Tier 1 equivalence testing. Specifically, FDA suggested using half of the total number of reference product lots to estimate $\sigma_R$ to maintain similar numbers of lots of both products when the number of reference product lots is much larger than the number of proposed biosimilar lots (e.g., more than 50 % more).**

**Since the teleconference on July 20, 2015, FDA's thinking has evolved, and we now recommend using all reference product lots to estimate the reference variability and the margin in equivalence testing. However, to reduce the potential impact of imbalance in sample sizes on the power, we recommend the following formula to calculate the confidence interval of the mean difference:**

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

**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 1-$\alpha$ quantile of the *t*-distribution with degrees of freedom *df** where *df** can be approximated by Satterthwaite method as follows**

$$df^* = \frac{\left(\frac{S_B^2}{n_B} + \frac{S_R^2}{n_R^*}\right)^2}{\frac{S_B^4}{n_B^2(n_B - 1)} + \frac{S_R^4}{\left(n_R^*\right)^2 (n_R - 1)}}$$

**If the number of biosimilar lots is 50% more than the number of reference lots, you can apply a similar approach as above with $n_T^* = \min(1.5 \times n_R, n_T)$ for the confidence interval calculation.**

***Question 5***

*The Applicant plans to submit a 351 (k) application containing a full data set from Phase I study in healthy subjects and from 78-week Phase III study which includes a randomized, double-blind period of 54 weeks (completed) and a transition-extension period of 24 weeks (on-going). As PK (Phase I study) and efficacy and safety (Phase III study – 54 week doubleblind, randomized period) profiles were shown to be similar between SB2 and the reference product, the Applicant believes that these study results present sufficient clinical evidence for similarity between SB2 and the reference product, provided that comparable safety profiles will be observed during the additional 24 week transition-extension period. Does the Agency have any comments?*

***Additional Clinical Question - Phase III Clinical Study Reports:***

*Phase III clinical study (SB2-G31-RA) have two distinct periods. The first study period was a 54 week of Randomized, Double-Blind period, followed by the second study period which is additional 24 weeks of Transition-extension period. Each 54-week and 78-week Clinical Study Report (CSR) includes the tables, listings and figures (TLFs) of 54-week and 78-week, respectively. Therefore, the Applicant plans to provide both 54-week CSR and 78-week CSR at the time of 351(k) submission. Does the Agency agree?*

*KC (Quintiles) Response: This question is confusing. Are these completely two different CSRs, one at 54 weeks and the other at 78 weeks? Please clarify as to what information will be included in the 78 CSR, is it only the transition data for the 24 weeks or does it include full study information from beginning to 78 weeks? Please clarify.*

*Samsung`s Clarification: The 78-week CSR include the full study information from beginning to 78 weeks, however, it only have tables, listings and figures (TLFs) from 54 weeks to 78 weeks as appendix. The TLFs from beginning to 54 weeks are included in 54-week CSR as appendix. Therefore, when FDA review the 78-week CSR and would like to look a table of 54 week, the CSR would be linked to 54-week CSR. This is the reason why Samsung have plan to submit both CSR at the BLA submission. The 78-week CSR is complete document which has introduction, study results and conclusion. It has 100-150 pages. The exception is only TLFs which are included as CSR appendix at the back of CSR pdf file.*

FDA response:

The proposed clinical data to support the 351(k) application seems reasonable. In the original question you specify that the transition-extension period of 24 weeks is on-going. However, in the additional question submitted via e-mail on November 12, 2015, you specify that you plan to submit the complete 78-week CSR. Clarify if the transition-extension period has been completed, i.e., if all the safety and immunogenicity data from that period will be submitted to the BLA.

*Samsung's emailed response:*

- *The transition-extension period has been completed.*
- *78-week CSR including all the safety and immunogenicity data from transition-extension period will be submitted at the time of a 351(k) application.*

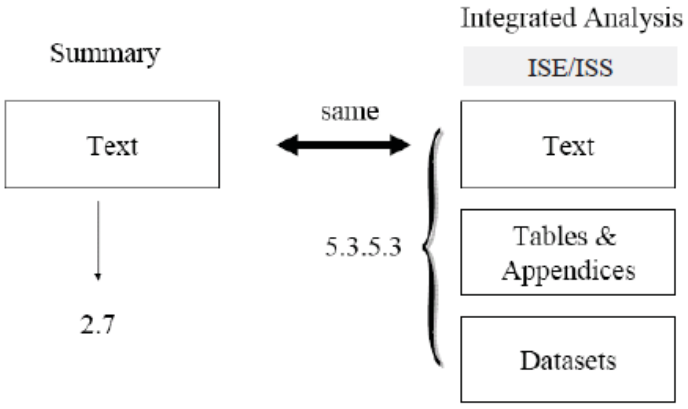
**Discussion:**
**FDA acknowledged Samsung's response.**

**In response to Samsung's inquiry as to whether single transition data could be included as part of the 120 Day Safety Update, FDA clarified that the BLA must be complete at the time of submission. This should include at least 6-8 weeks of comparative safety data following a single transition.**

*Question 6*
*The clinical study program of SB2 consists of two studies, a Phase I study in healthy 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 believes that the inclusion of ISE and ISS in the 351(k) application is not applicable for SB2. Does the Agency agree?*

FDA response:
We do not agree. As stated in the Guidance for Industry: *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* published in April 2009, the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) are detailed integrated analyses of all relevant data from clinical study reports, and should be located in Module 5. However, if you believe section 2.7.3 (Summary of Clinical Efficacy) and section 2.7.4 (Summary of Clinical Safety) would be sufficiently detailed to serve as the summary portion of the ISE and ISS, respectively, then you may 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. In this case, provide an explanation in both Module 2 and Module 5.

*Samsung's emailed response:*
- *In accordance with the Agency`s comments, the full ISE/ISS will be placed in Module 5 (section 5.3.5.3). The text portion of the ISE/ISS is repeated in Module 2 (section 2.7.3 and 2.7.4) as the Summary of Clinical Efficacy/Safety.*
- *TLFs and dataset which will be included in ISE/ISS are same with the TLF and dataset in the CSR without integration of Phase I and Phase III.*




**Discussion:**
**FDA stated that as long as the information will be submitted, Samsung's emailed proposal is reasonable.**

*Question 7*
*The Applicant plans to compose an eCTD dossier based on the core structure presented below. Does the Agency agree or have any comments?*

FDA response:
FDA agrees with your plan to submit an eCTD dossier as proposed.

*In addition, the Applicant requests the Agency's opinion on the following questions.*
*a) The Applicant plans to include assays of the in vitro biological activities (e.g. binding assays, cell-based assays, etc.) in the Quality section, and refer to it in the Non-clinical section, where applicable. Does the Agency agree with this approach?*

FDA response:
This approach is generally acceptable; however, use of hyperlinks to link in vitro biological activities in the Quality section to applicable parts of the Non-clinical section would facilitate our review.

*b) The Applicant plans to include a justification of extrapolation (for indications) mainly under 2.5.4. Overview of Efficacy, though the justification will be based on the similarity results of quality, non-clinical, and clinical studies along with relevant literature etc. Does the Agency agree with this approach?*

FDA response:
We recommend that you provide a separate document with your justification of extrapolation which can be submitted under Module 2.

If SB2 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:

- The mechanism(s) 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; 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)
- 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 infliximab 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 Remicade for the protected indication until the expiration of orphan drug exclusivity. Samsung 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 SB2 for the protected indication(s) until the orphan exclusivity expires.

*Samsung's emailed response:*

- *The Applicant acknowledges that the indication under orphan exclusivity will be approved after the orphan exclusivity expires.*
- *However, in accordance with Agency`s comments, the Applicant will provide the scientific justification for all indications of the reference product.*

**Discussion:**
**FDA stated that the justifications can be submitted in the BLA.**

*c) The Applicant plans to include CMC similarity data in 3.2.R.4.P. Furthermore, the Applicant plans not to submit 3.2.R.2.P – Comparability protocols, as it is an optional section for submission. Does the Agency agree with this approach?*

FDA response:
We do not agree. The protocol for the comparability assessment to demonstrate comparability between SB2 pilot, clinical and PVR batches, referenced in question 3, should be submitted in this section.

*Samsung's emailed response:*

- *The US FDA guidance 'Guidance for Industry, Drug Product, Chemistry, Manufacturing and Controls Information, Jan 2003' states that 'A comparability protocol is a protocol describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of post-approval manufacturing changes on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety and effectiveness of the drug product. Comparability protocols are optional'.*
- *Accordingly, the Applicant understands the 3.2.R.2.P section is for inclusion of comparability protocol for post-approval manufacturing changes. The Applicant would like to seek clarification from the Agency.*

**Discussion:**
**FDA stated that since a comparability protocol exists and was already utilized (as referenced in Question 3, the protocols should be submitted in an appropriate location in the BLA.**

**Samsung explained that similarity and comparability assessments were conducted as part of characterization protocols. Since one single uniform comparability protocol does not exist, they plan to include different assessments performed in other quality sections of the application.**

**FDA replied that the sponsor can include assessment protocols and provide hyperlinks.**

*d) The Applicant plans to include the Phase I CSR in Section 5.3.3.1 Reports of Human Pharmacokinetic (PK) Studies; Healthy Subject PK and Initial Tolerability Study Reports, rather than in Section 5.3.1 Reports of Biopharmaceutic Studies. Does the Agency agree with this approach?*

FDA response:
The full CSRs and the associated case report forms and data analysis of human pharmacokinetic and efficacy studies should be placed in Modules 5.3.3 and 5.3.5, respectively. 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 study should be in Module 5.3.1.4.

*e) The Applicant plans to include in 5.3.7 Case Report Forms only for death and withdrawals due to AEs in the eCTD at the time of 351(k) application. Case Report Forms for other subjects and individual patient listings will be available upon request. Does the Agency agree with this approach?*

FDA response:
We do not agree. In the 351(k) BLA, provide CRFs and narratives for all deaths, SAEs, AEs leading to discontinuation/withdrawal, and AEs of special interest.

*f) The Applicant does not plan to include non-applicable sections in the eCTD without justification. Does the Agency agree with this approach?*

FDA response:
Clarify what you mean by non-applicable sections. Note that the 351(k) BLA should be complete on initial submission and must contain all the information necessary to support a substantive review of the application.

*Samsung's emailed response:*

- *The 'non-applicable sections' are the sections which are not required for a biosimilar, including following examples, but not limited to;*
  - *Module 4*
    - *Safety pharmacology*
    - *Pharmacodynamic drug interactions*
    - *Genotoxicity*
    - *Carcinogenicity*
    - *Reproductive and development toxicity*
  - *Module 5*
    - *Bioavailability study reports*
    - *Reports of human pharmacodynamic studies*

**Discussion:**
**Samsung asked whether the sections above should include a justification for not conducting the studies or if the sections can be skipped.**

**FDA replied that it would be preferable to include a brief justification for each section not included.**

**FDA Post-meeting Note:**
**In slide 43/50, you described certain eCTD sections as "not required for a biosimilar." We do not necessarily agree with these examples given that section 351(k)(2)(A)(i)(I) of the PHS Act requires that a 351(k) application include information demonstrating that the biological product is biosimilar to a reference product based upon certain types of data. If you believe that certain sections in the**

**eCTD are not applicable to your submission of data to support a demonstration that your proposed product is biosimilar to the reference product, then we recommend that you provide a brief justification for the omission. FDA may determine, in FDA's discretion, that an element described in section 351(k)(2)(A)(i)(I) of the PHS Act is unnecessary in a 351(k) application.**

*Question 8*
*Since SB2 is developed as a biosimilar of Remicade®, and the similarity has been demonstrated from the quality, non-clinical and clinical studies, the Applicant plans to use the information in the PI of Remicade® to prepare the PI of SB2 in order to provide the sufficient information. The Applicant would like to seek the Agency's advice on this approach.*

FDA response:
With respect to your draft proposed labeling for SB2, 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 SB2 in PLR and PLLR format. 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 351(k) BLA.

***Additional Question - Format of study data/analysis programs:***
*Data analyses were performed using SAS Software. The Applicant plans to provide the Agency with all data in CDISC SDTM-format as a SAS transport files (XPT files) and a document including data set descriptions as well as variable descriptions (define.xml). These data will be provided in CTD Module 5 dataset folder. Does the Agency agree?*

FDA response:
Your plan for the raw data submission appears reasonable. However, we also expect that you submit analysis datasets (preferably in CDISC ADaM-format) containing all derived variables, with proper data definitions and SAS programs used for the derivation and for key analyses.

*Samsung's emailed response:*
*The Applicant will include the following three items along with SDTM datasets and its define.xml in CTD Module 5 dataset folder;*
*(1) ADaM datasets*
*(2) define.xml for proper data definitions and derivations of ADaM datasets*
*(3) SAS program used for the creation of ADaM datasets*

**Discussion:**
**FDA stated that the sponsor's plan seemed reasonable, although the SAS programs for key analyses should also be submitted to facilitate FDA review.**

**Additional Statistical Comments:**

- Your primary analysis for Study SB2-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 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.

  *Samsung's emailed response:*
  - *Overall 584 patients (RAN) were randomized into Phase III study and 583 patients were included in the full analysis set (FAS) in which one patient was excluded from RAN due to withdrawal prior to the first injection. 54-week CSR included the primary analysis for both FAS and per-protocol set (PPS). The Applicant believes that this approach reflects the Agency`s recommendation.*
  - *54-week CSR reported 95% confidence interval (CI) for the difference in ACR20 responses but the Agency requested 90% CI for the difference in ACR20 responses in the package. Therefore the Applicant will modify NparCov SAS macro to get 90% CIs for the difference in ACR20 for FAS and PPS and report them in the Module 5 ISE and Module 2 section 2.7.3.*

  **Discussion:**
  **FDA noted agreement.**

- In preliminary comments for a BPD Type 3 meeting on March 24, 2014, we recommended that you continue collecting safety and efficacy data through the time point of all key comparisons, even in patients who discontinued the study treatment, to help prevent missing data in intention-to-treat analyses. Please clarify whether you followed the recommendation in the comparative clinical study, and have such data available for analyses.

  *Samsung's emailed response:*
  - *Following the Agency`s recommendation, the Applicant collected efficacy and safety data as long as they continued the Phase III study for patients who have had a major protocol deviation.*
  - *For patients who discontinued the investigational product (IP), the Applicant collected efficacy data at the time of discontinuation and safety data up to 8 weeks from last administration of IP to confirm the patient safety.*

  **Discussion:**
  **FDA acknowledged the clarification.**

- It appears that approximately 15-20% of patients dropped out of the study before Week 30-54 assessments. We don't believe that the sensitivity analyses discussed in the meeting package will sufficiently explore the potential effect of violations in the assumptions about missing data 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 SB2 arm had dissimilar outcomes than dropouts on the EU-Remicade 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.

*Samsung's emailed response:*
*Prior to Week 30, 37 patients from SB2 and 28 patients from Remicade® were discontinued from Phase III study. The Applicant will perform a tipping point analysis with these patients to compare the equivalence margin of 15% (or lower margin of -12%) with 95% or 90% confidence interval for the difference in ACR20 at Week 30.*

**Discussion:**
**FDA noted agreement.**

**Nonclinical comment**:
As communicated in meeting minutes dated March 5, 2012 and follow-up comments dated May 15, 2012, your proposed studies of FcγRIIIa binding should assess both of the 158F/V polymorphisms of FcγRIIIa. The literature suggests that there may be a functional difference between alleles polymorphic at the 158 V/F residue. If SB2 binds differently than infliximab to a polymorph that is associated with disease, you would have to justify how this result does not preclude a finding that SB2 is highly similar to US-licensed Remicade. If you choose not to do a binding assay comparing binding of FcγRIIIa variants at the 158V/F position, provide a clear rationale detailing why a binding assay is unnecessary.

*Samsung's emailed response:*
- *The Applicant has performed FcγRIIIa binding studies with V/V, F/F, and V/F variants at the 158 position.*
- *The study results will be provided in the 351(k) application.*

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

**Additional CMC comment:**
The total protein content of SB2 appears to be about (b) (4)% higher than the amount measured in vials of US-licensed Remicade. A control strategy for the SB2 drug product should be developed to more closely match the amount measured in US-licensed Remicade.

*Samsung's emailed response:*
- *The Applicant would like to clarify that the difference observed is due to the different methods used to determine volume during calculation of protein content.*

- *In Table 92, the content of SB2 (mean (b) (4) mg/vial) was calculated by using volume experimentally determined by the extract volume measurement, whereas the content of US Remicade® (mean (b) (4) mg/vial) was calculated using the nominal volume of 10 mL.*
- *Based on the QC results from 8 lots of SB2 DP which were calculated using nominal volume, the mean protein content was (b) (4) mg/vial, which was similar to that of US Remicade® ( (b) (4) mg/vial)*

| Test | Volume used for calculation | Clinical DP | | | | | PVR DP | | | Mean | SD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | P49202A | P49203A | P49204A | P49205A | P49208A | SB2-DP-14001 | SB2-DP-14002 | SB2-DP-14003 | | |
| Protein content ($A_{280}$) (mg/vial) | Nominal volume (10 mL) | | | | | | | | | | (b) (4) |
| | Actual extractable volume | | | | | | | | | | |

**Discussion:**

**FDA noted that these were new data emailed the morning of the meeting, and the Agency did not have sufficient time to thoroughly review the information. FDA stated that the same method should be used to compare the two products, and that the biosimilar product should also match the protein content of the reference product. If the (b) (4) % difference in protein content is real, the sponsor should consider revising the fill process set points to more closely match Samsung's measurement of protein content in the reference product. Data to support the proposal should be submitted with the BLA.**

**Additional Question - BIMO Inspection related documents:**

*The Applicant plans to provide the information for BIMO inspection at the time of 351(k) submission, as follows.*

- *Part I. Tabular Listings of Site Information will be provided as located in study folder in Module 5.*
- *Part II. Line Listing by Site will not be provided, since the complete subject-level data listings will be provided in the appendix of the CSR.*
- *Part III. Site-Level Data Set will be provided as located in "dataset>bimo>site-level" folder in Module 5*

*Does the Agency agree?*

FDA response:

We agree. Refer to "Office of Scientific Investigations (OSI) Requests" section below.

**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.

*Samsung's emailed response:*

- *The revised iPSP in accordance with the FDA comments will be submitted in Dec 2015.*
- *After the agreement on iPSP is reached, PSP will be submitted at the 351(k) application.*

**Discussion:**

**Samsung added that safety data about US-licensed Remicade use in children 17 years of age and younger with psoriasis is not readily available. They asked if FDA was**

**requesting a general rationale or specific data for the waiver justification for children with psoriasis.**

**FDA replied that the justification can be a general rationale instead of specific data, and should take into consideration the FDA advice provided to the iPSP on handling PREA requirements for plaque psoriasis.**

## ADDITIONAL DISCUSSION

**Samsung asked about using a similarity margin (SM) of ±15% for the comparative clinical study in patients with RA, instead of a SM with lower bound no greater than 12% magnitude.**

**FDA responded that the Agency's current thinking is a 12% SM. As relayed in past interactions with the sponsor, a 15% SM is not acceptable (refer to meeting minutes dated February 4, 2013, and April 25, 2014).**

**Samsung noted that they plan to submit the 351(k) BLA in March 2016. SB2 has been approved in South Korea, has been submitted for EMA review, and will be submitted for review in Canada and Australia.**

## 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.

**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.

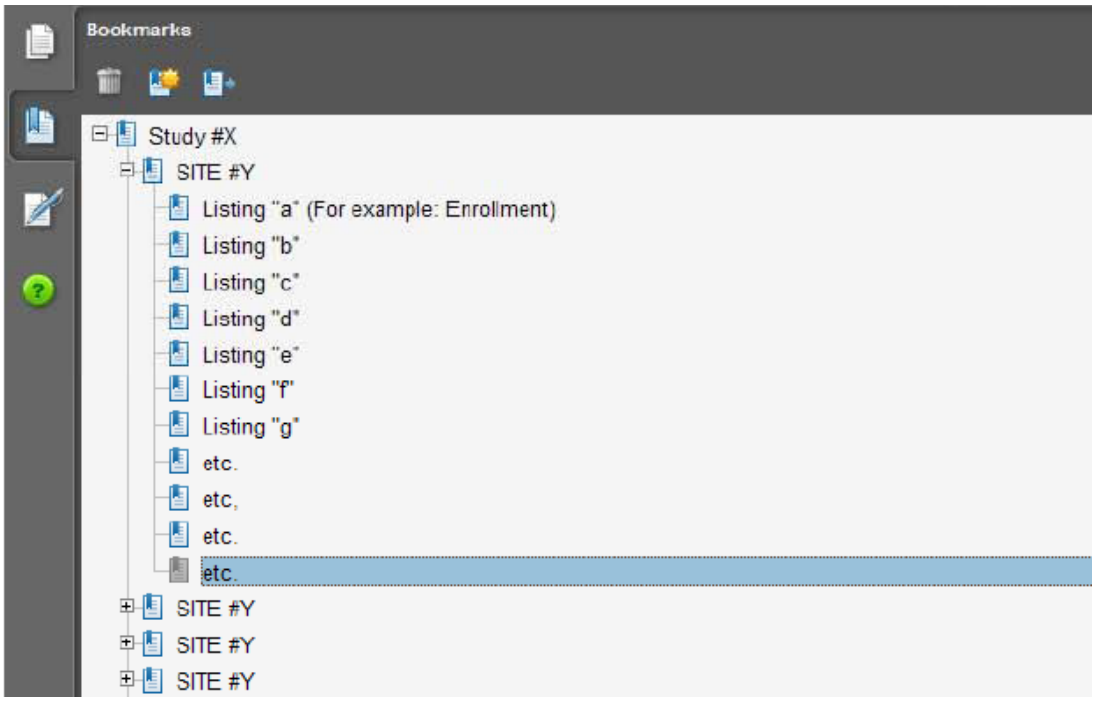
4. For each clinical study, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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

**ISSUES REQUIRING FURTHER DISCUSSION:**

There were no issues requiring further discussion.

**APPENDIX (begins next page):**

Samsung's emailed responses (slides) sent morning of Monday, December 14, 2015.

27 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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/s/

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CHRISTINE H CHUNG
02/23/2016
Christine Ford (formerly Chung)