CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761058Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110467

MEETING MINUTES

Boehringer Ingelheim
900 Ridgebury Rd
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Christopher Dougherty, PhD, MS
Senior Associate Director

Dear Dr. Dougherty:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BI 695501.

We also refer to the meeting between representatives of your firm and the FDA on June 15, 2016. The purpose of the meeting was to obtain feedback and agreement on your proposed structure, format, and content of an application for BI 695501 under Section 351(k) of the Public Health Service Act (PHS Act).

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) 796-2777.

Sincerely,
{See appended electronic signature page}

Sadaf Nabavian, PharmD
Sr. Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Biosimilar
Meeting Category:	Biosimilar Biological Product Development (BPD) Type 4
Meeting Date and Time:	June 15, 2016, from 3:00-4:00 p.m. EST
Meeting Location:	White Oak Building 22, Conference Room: 1419
Application Number:	IND110467
Product Name:	BI 699501 (a proposed biosimilar to US-licensed Humira)
Indication:	BI 699501 is being developed for the same indications as approved for US-licensed Humira
Sponsor:	Boehringer Ingelheim (BI)
Meeting Chair:	Badrul A. Chowdhury, MD, PhD
Meeting Recorder:	Sadaf Nabavian, PharmD

FDA ATTENDEES

Badrul A. Chowdhury, M.D, Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, M.D., Associate Director, DPARP
Nikolay Nikolov, M.D., Clinical Team Leader, DPARP
Rachel Glaser, M.D., Clinical Reviewer, DPARP
Anshu Marathe, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II, OCP
Carlos Mena-Grillasca, Pharm.D., Safety Evaluator, OSE/DMEPA
Mishale Mistry, Pharma.D., Team Leader, OSE/DMEPA
Lei He, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, OCP
Steven Fong, Ph.D., Microbiology Reviewer, OPQ/OPF/DIA/IABI
Susan Kirshner, Ph.D., CMC Supervisor, OPQ/OBP/DBRRIII
Howard Anderson, Ph.D, CMC Reviewer, OPQ/OBP/ DBRRII
Robert Meyer, Ph.D., Reviewer, Center for Devices and Radiological Health
Gregory Levin, Ph.D., Statistical Team Leader, OTS/OB/DBVII
Carol Galvis, PhD, Pharmacology/Toxicology Acting Team Leader, DPARP
Lawrence Leshin, PhD, Pharmacology/Toxicology Reviewer, DPARP
Sue Lim, M.D., Senior Staff Fellow, Office of New Drugs (OND), Therapeutic Biologics and Biosimilars Staff (TBBS)
Stacey Ricci, MEng, ScD, Senior Toxicologist, OND, TBBS
Daniel Orr, MA, JD, Regulatory Counsel, Office of Regulatory Policy, Division of Regulatory Policy I
Sadaf Nabavian, PharmD, Senior Regulatory Project Manager, DPARP

SPONSOR ATTENDEES
Benita von Glahn, PhD, Head of Regulatory Affairs Biosimilars and Immunology, Global Department Biosimilars
Christopher Dougherty, PhD, Senior Associate Director, US Regulatory Affairs Biosimilars
Stephanie Glaser, PhD, Regulatory Affairs Biosimilars Development, Global Regulatory Affairs
Huiping Jiang, PhD, Director, US Regulatory Affairs Biosimilars
Malou Gemeniano, PhD, CMC Strategy and Technical Regulatory Affairs
Florian Lengyel, PhD, Global CMC Strategy and Technical Regulatory Affairs
Deepak Assudani, MD, Clinical Program Leader, Corporate Division Medicine, Therapeutic Area Biosimilars
David Hall, PhD, Immunology Therapeutic Area Statistical Expert

1.0 BACKGROUND

BI submitted a BPD Type 4 Meeting Request on March 23, 2016, for BI 695501, a proposed biosimilar to US-licensed Humira.

The FDA's preliminary comments were sent to BI on June 13, 2016. After review of these comments, BI stated their intent to continue with the meeting as scheduled and requested to discuss the FDA's responses to Questions 7, 10, 13, 14, 16, OSI package, 5, 2, and 6, in that order. For the meeting, BI provided their follow-up responses to FDA's response prior to the meeting with a slide presentation, from which BI's response is captured in the meeting minutes and some of the information provided in the slides has been incorporated in the discussion sections under the questions noted above. The slides are included in Section 6, Attachments and Handouts.

The questions from BI are in bold italic, FDA's responses to the questions are in italic, BI's follow up responses are in bold and any discussion that took place between BI and the FDA are in regular font.

FDA may provide further clarifications of, or refinements and/or changes to the responses and the advice provided at the meeting based on further information provided by BI and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

2. DISCUSSION

QUESTION 1:

Does the Agency have any comments about the general organization of Module 3 and related CMC documents in the planned BLA for BI 695501? The applicant requests the Agency's advice on any additional documents required under section 351(k) of the Public Health Service Act.

FDA Response:

We are providing the following product quality microbiology comments for you to consider for the preparation of your 351(k) BLA submission:

a. *All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in Module 1 of the*

BLA to facilitate the planning of the pre-license inspections during the review cycle. Include a complete list of the manufacturing and testing sites with their corresponding establishment registration number (FEI) number.

b. *The Chemistry, Manufacturing, and Controls (CMC) Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to, the following:*

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

   II. *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 (3.2.S.2.5).*

   III. *Information and summary results data demonstrating microbial control after column resin and UF/DF membrane sanitization during reuse and storage (3.2.S.2.5).*

   IV. *Bioburden and endotoxin data obtained during manufacture of at least three conformance lots (3.2.S.2.5).*

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

   VI. *Drug substance (DS) bioburden and endotoxin release specifications (3.2.S.4).*

   VII. *Summary report and results from bioburden and endotoxin test methods qualification performed for in-process intermediates and the drug substance (3.2.S.4). In addition, the test methods should be described.*

   VIII. *If the formulation contains polysorbate, the effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance during hold. Effects of sampling containers on endotoxin recovery should also be evaluated (3.4.S.4).*

c. *The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support* (b) (4) *sterility assurance. 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" at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.*

   Provide the following information in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:

   I. *Description of the manufacturing areas and fill line, including air classifications.*

II. *Description of the environmental and personnel monitoring programs.*

III. *Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.*

IV. *Description of the sterilizing filter (supplier, membrane material, membrane surface area, etc.), the pressure limit or flow rate limit for sterilizing filtration, and the acceptance criterion for post-use integrity testing.*

V. *Parameters for filling and stoppering.*

VI. *Processing and hold time limits, including the time limit for sterilizing filtration.*

d. *The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:*

I. *Bacterial filter retention study for the sterilizing filter.*

II. *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.*

III. *In-process microbial controls and hold times. Three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.*

IV. *Pre-sterile filtration bioburden limits should be monitored and should be less than 10 CFU/100 mL.*

V. *Isolator decontamination, if applicable.*

VI. *Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.*

VII. *A description of the routine environmental monitoring program.*

VIII. *Shipping validation studies, including container closure integrity data. The effects of varying air pressure on syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data that*

demonstrate that the syringe plunger movement during air transportation does not impact product sterility.

IX. *Assembly validation studies, including container closure integrity data. The study should demonstrate that the assembly processes for the pre-filled syringe* (b) (4) *do not impact product sterility.*

e. *The following method validation information should be provided:*

I. *Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the pre-filled syringe should be included. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. We recommend that container closure integrity testing be performed in lieu of sterility testing for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2).*

II. *Summary report and results for 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.*

III. *Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13 (b).*

IV. *Formulations with certain excipient and polysorbate combinations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of standard endotoxin (CSE or RSE) into undiluted in-process samples (if applicable) and the drug product and then testing for recoverable endotoxin over time. These studies should be conducted in the containers in which the product and samples are held prior to endotoxin testing.*

From the product quality perspective, the remainder of the proposed organization of CMC documents in the eCTD appears appropriate. The remainder of the proposed information appears sufficient to support the submission of a 351(k) BLA.

Discussion:

No discussion took place.

QUESTION 2:

Does the Agency concur with the approach and the location of device related documents included in the BLA submission?

FDA Response:

No, provide all HFE/UE reports (i.e. pre-filled syringe (b) (4) *) in eCTD section 5.3.5.4 – Other Study reports and related information. The remainder of the device related documents are proposed to be located in the appropriate sections.*

Discussion:

(Slide 13)

BI agreed to provide the HFE/UE reports in section 5.3.5.4 and will include the device related documents in module 3. BI stated that the PFS design control document will be provided during the prior approval inspection. BI sought clarification on FDA's expectation on the post-approval changes (b) (4) whether they should follow the FDA guidance for industry titled, "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products" (1997) and "Changes to an Approved NDA or ANDA". The FDA replied yes.

QUESTION 3:

Does the Agency agree with the number and the selection of executed batch records for the BLA submission?

FDA Response:

Yes, the following batch records should be submitted in the BLA for review.

1) *A single EBR for Drug Substance at BIFI.*
2) *A single EBR for Drug Product pre-filled syringe at BIFI.*
3) (b) (4)
4) *A single EBR for Drug Product pre-filled syringe at* (b) (4)

Discussion:

No discussion took place.

QUESTION 4:

Does the Agency agree that Boehringer Ingelheim can submit additional stability data with the four-month safety update to further support the proposed shelf life?

FDA Response:

Yes, we agree that additional data can be submitted during the BLA review to support shelf life. The determination of shelf life is made during the BLA review and is based on real time stability data as per ICHQ5C.

We note that a 24 month shelf life is being proposed for both drug product presentations. At least 6 months of real time stability data on at least 3 batches in the same final container closure system, representative of the commercial manufacturing process and scale, are needed to establish a dating period. Leveraging stability data from lots manufactured at BIP prior to the proposed commercial process) is dependent upon how representative the BIP process is to the two proposed commercial processes BIFI and (b) (4) *and a demonstration of comparability between BI 699501 manufactured at BIP and BIFI/* (b) (4) *Functional attribute testing of the autoinjector should be part of the stability program.*

Additional Comment

(b) (4)

Discussion:

No discussion took place.

QUESTION 5:

BI proposes to include comparability protocols in the BLA submission (b) (4) ***. Does the Agency agree?***

FDA Response:

The proposal to include 3 comparability protocols in the original BLA for review regarding, (b) (4)

Discussion:

(Slide 12)

(b) (4)

(b) (4)

[redacted]

QUESTION 6:

Does the Agency have any comments about the general organization and/or proposed content of nonclinical information to be included in the 351(k) BLA?

FDA Response:

The proposed organization and content of the nonclinical information appear appropriate.

Discussion:

(Slide 14)

BI noted that all the pharmacological assays carried out for BI 695501 are described in the similarity assessment report located in module 3.2.R. and that all the pharmacological written summaries (2.6.2) will contain links to the detailed information in the similarity assessment report for the assays and asked if the proposed approach is reasonable. The FDA accepted BI's proposal as stated that as long the relevant sections are appropriately cross-referenced then that should be acceptable.

QUESTION 7:

Does the Agency have any comments regarding the location of the Module 5 documents in the eCTD, especially in regard to those mentioned in the Company position below?

FDA Response:

Overall, the proposed content for module 5 appears reasonable.

We note that in the current briefing package, you propose to include an integrated immunogenicity summary; however, you have not provided details on the immunogenicity data to be submitted in the initial BLA. As previously communicated in our responses dated November 18, 2015, safety and immunogenicity data for all patients receiving treatment for at least eight weeks following the single

transition at Week 24, with the randomization status for all patients, are expected in the original 351(k) BLA submission. We remind you that your application should be complete upon submission, meaning that all efficacy and safety data that you consider necessary for approval should be included with the initial submission.

We also note your proposal to include the indication extrapolation justification in eCTD Module 5.3.5.4. This appears reasonable. Please note that Section 351(k)(2)(A)(i)(II) of the PHS Act requires that a 351(k) application for a proposed biosimilar product include information demonstrating that the proposed biosimilar product and the reference product utilize the same mechanism or mechanisms of action for the condition(s) of use for which licensure is sought, but only to the extent that the mechanism(s) of action are known for the reference product. In FDA's draft guidance for industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (2012), we explain: "If the clinically relevant mechanism(s) of action are known for the reference product or can reasonably be determined, one or more of the functional assays should reflect these mechanisms of action to the extent possible." Accordingly, in your BLA submission provide functional assays, including mechanism(s) of action, comparing BI 695501 to the reference product (US-licensed Humira) and include a justification that BI 695501 utilizes the same mechanism(s) of action as US-licensed Humira. This data and information should not be limited to the "primary" mechanism of action if other mechanism(s) of action are known or can reasonably be determined. Your indication extrapolation justification should link to the relevant section(s) of Module 3.

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. The full CSRs and the associated case report forms and data analysis data of comparative bioavailability and bioequivalence study, human pharmacokinetic, and efficacy studies should be placed in Modules 5.3.1, 5.3.3 and 5.3.5, respectively.

(b) (4)

Discussion:

(Slides 3 and 4)

BI clarified that the initial 351 (k) submission will include safety data up to the cut-off date which will be when the last patient reaches Week 32 and will include safety data for at least 8 weeks after the single transition at Week 24. BI also plans to submit an integrated summary of immunogenicity in module 5.3.5.3 and will include discussion on suitability of bioanalytical methods and summary of immunogenicity results from the individual clinical studies. BI added that they will include the immunogenicity data for patients that have reached the Week 40 visit at the time of the Week 32 cut-off. BI included a table indicating that they anticipate available safety and PK results from 593 patients at Week 24 visit (before single transition) and 475 patients at visit Week 40 (after single transition). The FDA replied that their proposal seemed acceptable. The FDA requested that BI provide the disease characteristics and immunogenicity data at Week 24 as a baseline prior to the single transition. The integrated summary of immunogenicity should include an assessment of anti-drug antibodies and neutralizing antibodies, as well as the impact of immunogenicity on safety, efficacy, and PK for at least the first 24 weeks of the study. FDA asked how many patients would undergo the transition. BI clarified that immunogenicity data from approximately 120 patients who undergo a single transition to BI 695501, in addition to 120 patients who remain on the comparator product, would be provided in the 351 (k) BLA submission.

BI accepted the rest of FDA's responses and recommendations pertaining to the content of the document and the appropriate locations.

(Slide 5)

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Clarifying Question for FDA:

(b) (4)

QUESTION 8:

Does the Agency agree with BI's proposal for eCRFs to be provided in the BLA submission?

FDA Response:

The proposed set of eCRFs is reasonable. As advised in our written responses dated November 11, 2015, the corresponding patient narratives should also be submitted.

Discussion:

No discussion took place.

QUESTION 9:

Does the Agency concur with the proposal on the electronic format of study data to be included in the BLA submission?

FDA Response:

Yes, we concur with your proposal for submission of electronic datasets, documentation, and SAS programs.

Discussion:

No discussion took place.

QUESTION 10:

Does the Agency concur with the proposed data cut-off date and the scope of data to be included in the Four-Month Safety Update?

FDA Response:

No, we do not concur. In the current briefing package, you note that while the last patient should have completed the Week 58 assessment, the final study report will not be complete at the time of the 4 month safety update. You propose to include selected safety data up to week 58, but this will not include any immunogenicity data. This proposal is different from your response to the FDA written advice dated November 18, 2015. Specifically, in that response you proposed the following:

> *"BI Response to Question 1a:*
> *In order to fulfill FDA's request to include safety data for all patients at week 32 into the initial BLA, BI proposes to move the data cut-off for the primary analysis report to the time point when all patients in the study have completed the week 32 assessment and to provide the following in the initial 351(k) BLA for BI 695501:*
>
> - *Fully unblinded week 24 data, as discussed in the Type 2 briefing package, according to initial randomization.*
> - *Fully unblinded adverse event data for all subjects at week 32, according to initial randomization as well as re-randomization status.*
> - *Fully unblinded safety (AE and lab data) and immunogenicity data for all patients who completed the week 40 visit at the time of data cut-off. BI expects that data will be available for a substantial number of patients, i.e. week 40 data will be available for approximately 480 patients (75% of all randomized patients not considering drop-outs) at this point. This would enable the comparison of safety and immunogenicity data for approx. 120 patients in the Humira-BI 695501 transition arm with approx. 120 patients in the continuous Humira arm.*
> - *BI also commits to submit for the entire study (up to week 58) fully unblinded safety and immunogenicity data in the form of outputs and listings at the 120 day safety update time point (see Response to Question 1 b).*
>
> *BI Response to Question 1b:*
> *As discussed above, BI proposes to provide full clinical trial data for study 1297.2 as part of the 120 day safety update to FDA. This will include fully unblinded outputs and data listings for safety and immunogenicity for all patients until end of study (week 58)."*

Clarify the discrepancy with the current proposal. Also, we remind you that your application should be complete at the time of submission, meaning that all efficacy, safety, and immunogenicity data necessary to support approval should be included with the initial 351(k) BLA submission for our review. Safety and immunogenicity data for all patients receiving treatment for at least eight weeks following the single transition at Week 24 is expected in the original 351(k) BLA submission.

Your proposal to include safety data in selected outputs for studies 1297.6 and 1297.11 in the 120 day safety update is reasonable.

Discussion:

(Slide 7)

BI proposed including the following data as part of a 4-month safety update:

- Study 1297.2-Fully unblinded safety and immunogenicity data up to Week 58 in the form of selected outputs and listings will be submitted.

- Studies 1297.6 and 1297.11-BI will include safety data in selected outputs.

- Study 1297.3-At the time of 4-month safety update, BI will provide available line listings for SAEs from BI's safety database for this ongoing open-label study.

FDA accepted BI's proposal.

QUESTION 11:

Boehringer Ingelheim understands that inclusion of a REMS for BI 695501 in the BLA submission would not be required, as US-licensed Humira has no active REMS and no specific risk mitigation activities. Does the Agency concur?

FDA Response:

In December 2011, FDA released Humira from its previously approved REMS (refer to the letter posted under the approval history for US-licensed Humira at Drugs@FDA with the action date December 13, 2011). The FDA has also 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 21CFR 208.1" (refer to the letter posted under the approval history for US-licensed Humira at Drugs@FDA with the action date July 13, 2011). Accordingly, at this time, developing a Medication Guide for patients would be appropriate for your proposed biosimilar product. 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 and/or Medication Guide during the review of your application.

Discussion:

No discussion took place.

QUESTION 12:

Does the Agency concur with the proposed product packaging configurations for BI 695501 to be included in the 351(k) BLA?

FDA Response:

Yes, your proposal appears reasonable.

Discussion:

No discussion took place.

QUESTION 13:

Does the Agency concur that the BI 695501 US PI is to be based on the current US PI of the US-licensed Humira along with the noted changes?

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 BI 695501 in Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) format. See also our Response to Question 14. 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.

Discussion:

BI proposed to submit the annotated prescribing information (PI) as a single tracked change document showing differences of BI's proposed biosimilar, BI 695501, to the US-licensed Humira PI, as well as the source of all data and information presented. Per the FDA draft guidance noted in our response, FDA asked that BI submit a tracked changes and annotated version of the proposed biosimilar product PI that explains the differences from the US-licensed Humira PI, and clean versions of both the Humira PI and the proposed PI for BI 695501. The FDA also asked that BI submit three proposed suffixes composed of four lowercase letters that can be attached to the core name "adalimumab" as part of the BLA submission. The FDA will provide a post-meeting note regarding which module to include the proposed suffixes.

FDA Post-meeting note:

Proposed suffixes can be submitted in Module 1 under *1.12.4 Request for comments and advice*. The leaf should be labeled as "Request for Review of Suffixes for Proper Name."

QUESTION 14:

Does the Agency agree with BI's proposal to submit a request for a deferral for the PLLR format and content requirements?

FDA Response:

No, we do not agree. As you note, the Pregnancy and Lactation Labeling Rule was implemented on June 30, 2015. You intend to submit a BLA on or about October 20, 2016, and therefore, you must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. 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:

1. *The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products*
2. *The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential*
3. *Regulations and related guidance documents*
4. *A sample tool illustrating the format for Highlights and Contents*

5. *The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances*

6. *FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading*

Discussion:

(Slide 9)

BI noted that they will submit proposed labeling that is consistent with the PLLR requirements based on US-licensed Humira approved labeling. FDA requested that BI submits their proposed labeling in PLLR format and that it will be a review issue and up for discussion during the labeling review cycle.

Post-meeting note:

The FDA refers BI to the PLLR formatting for Humira USPI approved on June 30, 2016.

QUESTION 15:

Does the Agency concur with the proposal to provide a BI 695501 product specific IFU?

FDA Response:

Yes, we agree.

Discussion:

No discussion took place.

QUESTION 16:

Does the Agency concur with BI's assumptions regarding a potential Advisory Committee for BI 695501?

FDA Response:

A final determination on the need for an Advisory Committee meeting will be made during review of the BLA submission.

Discussion:

(Slide 10)

BI sought clarification on the timeline of review and some of the milestone meetings during the BLA review cycle. The FDA replied that the initial 351 (k) BLA will be under a 10-month review clock and that by Day 60 the FDA will inform BI the status of filing and by Day 75 a filing letter with or without filing issues/comments will be issued. BI inquired on expected communications during the review cycle

such as a mid-cycle meeting. The FDA replied that typically mid-cycle communication takes place; in addition, at any time point during the review cycle the team will convey comments or request information as necessary.

Additional Discussion:

At the end of the meeting, FDA requested data on reverse signaling and that more information will be forthcoming as a post-meeting note.

FDA post-meeting note:

Please refer to our communication dated July 14, 2016.

3.0

PREA REQUIREMENTS

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

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

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

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

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

PRESCRIBING INFORMATION

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

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

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

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study

data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all clinical studies used to support a demonstration of no clinically meaningful differences between the proposed biosimilar biological product and the reference product in the application. Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

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

d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the 351(k) BLA for each of the completed clinical studies:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

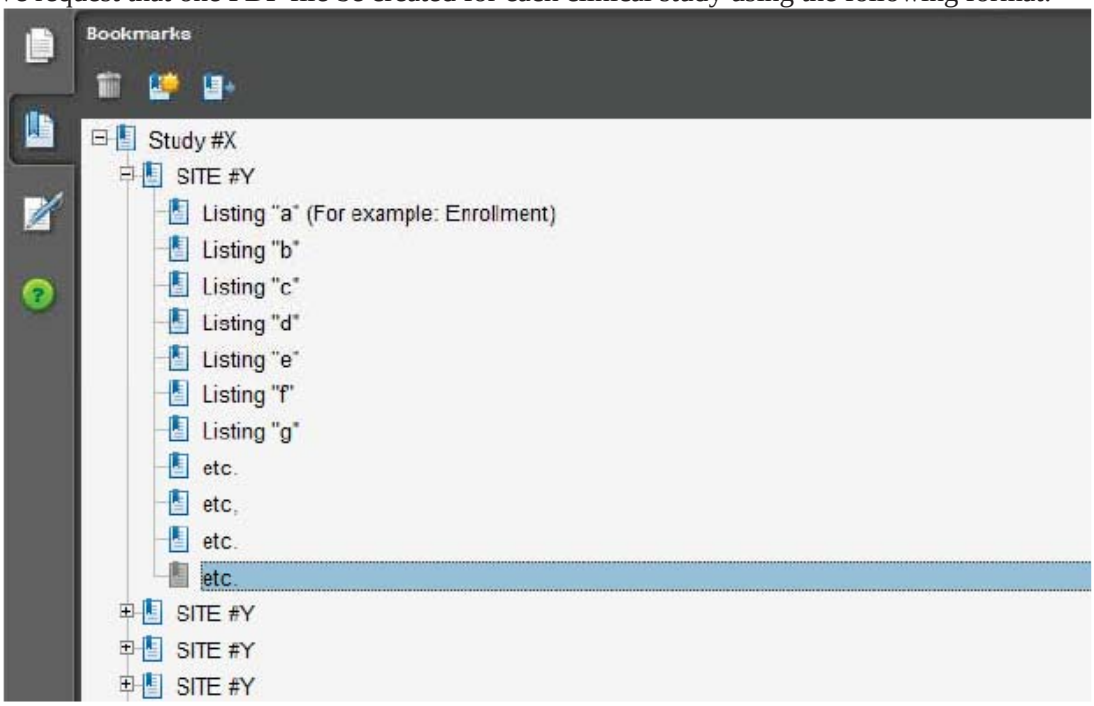
3. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND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

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

II. Request for Subject Level Data Listings by Site

1. For each clinical study: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the 351(k) BLA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the clinical studies)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each clinical study using the following format:



III. Request for Site Level Dataset:

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION
None

5.0 ACTION ITEMS
None

6.0 ATTACHMENTS AND HANDOUTS
BI's slide deck

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

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

/s/

SADAF NABAVIAN
08/10/2016