CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761255Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 124098

MEETING MINUTES

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, IL 60047

Attention: Navayath Shobana, PhD
Director, Regulatory Affairs

Dear Dr. Shobana:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MSB11022.

We also refer to the telecon between representatives of your firm and the FDA on October 4, 2021. The purpose of the meeting was to discuss the overall content and format of a planned dossier for future filling of your application via the 351(k) BLA regulatory pathway.

A copy of the official minutes of the telecon 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
CDR, US Public Health Service
Rheumatology and Transplant Medicine
Division of Regulatory Operations - Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Biosimilar
Meeting Category:	BPD Type 4
Meeting Date and Time:	October 4, 2021; 12:00-1:00 PM ET
Meeting Location:	Teleconference
Application Number:	IND 124098
Product Name:	MSB11022
Indication:	MSB11022 is being developed for the same indications as those approved for US-licensed Humira
Sponsor:	Fresenius Kabi USA, LLC
Regulatory Pathway:	351(k) of the Public Health Service Act
Meeting Chair:	Nikolay P. Nikolov, MD
Meeting Recorder:	Sadaf Nabavian, PharmD

FDA ATTENDEES

Nikolay P. Nikolov, MD, Director, Division of Rheumatology and Transplant Medicine (DRTM), Office of Immunology and Inflammation (OII), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER)

Juwaria Waheed, MD, Clinical Reviewer, DRTM, OII, OND, CDER

Melinda McCord, MD, Clinical Reviewer, DDD, OII, OND, CDER

Ping Ji, PhD, Clinical Pharmacology Team Leader, Division of Inflammation and Immune Pharmacology (DIIP), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)

Kathleen Fritsch, PhD, Mathematical Statistical Reviewer, Division of Biometrics III (DBIII), Office of Biostatistics (OB), OTS, Center for Drug Evaluation and Research (CDER)

Mohamed Alosh, PhD, Statistical Team Leader, DBIII, OB, OTS, CDER

Leslie Ann Rivera Rosado, PhD, Product Quality Team Lead, Office of Biotechnology Products (OBP), Office of Pharmaceutical Quality (OPQ), CDER

Marlene Schultz-Depalo, MS, MA, RAC, OBP-IO Biosimilar Program and Policy Analyst, OBP, OPQ, CDER

Jason Flint, MBA, PMP, Social Scientist/Human Factory, Office of Surveillance and Epidemiology (OSE), CDER

Sandhya Apparaju, PharmD, Clinical Analyst, Division of Gastroenterology (DG), OII, OND, CDER

Sun Seo, MD, Clinical Team Leader, DG, OII, OND, CDER

Emanuela Lacana, PhD, Deputy Director, CDER, OND, Office of Therapeutic Biologics and Biosimilars (OTBB)

Alison Falb, Regulatory Counsel, CDER, OND, OTBB, Policy Staff

Cristina Ausin, PhD, Reviewer, CDER, OND, OTBB, Scientific Review Staff (SRS)

Sarah Schrieber, PharmD, Reviewer, CDER, OND, OTBB, SRS

Stacey Ricci, MEng, ScD, Director, CDER, OND, OTBB, SRS

Sarah Brown, PharmD, Science Policy Analyst, CDER, OND, OTBBS, SRS

Sadaf Nabavian, PharmD, Sr. Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation (DROII), Office of Regulatory Operations (ORO), OND, CDER

SPONSOR ATTENDEES

Alexandr Meszaros	Fresenius Kabi SwissBioSim GmbH	Director, Clinical Safety and Pharmacovigilance
Elvira Klissourska	Fresenius Kabi SwissBioSim GmbH	Senior Director, Clinical Affairs, Clinical Operations
Joelle Monnet	Fresenius Kabi SwissBioSim GmbH	Director, Biostatistics Clinical Development
Ina Frank	Fresenius Kabi SwissBioSim GmbH	Vice President, Regulatory Affairs
Julia Lehner	Fresenius Kabi SwissBioSim GmbH	Regulatory Affairs Specialist

Klemen Spaninger	Fresenius Kabi SwissBioSim GmbH	Senior Director, Global Program Lead
Martin Ullmann	Fresenius Kabi SwissBioSim GmbH	Senior Director, Clinical Pharmacology, Scientific Affairs and Immunogenicity
Navayath Shobana	Fresenius Kabi USA, LLC	Director, Global Regulatory Affairs
Yijian Chen	Fresenius Kabi SwissBioSim GmbH	Director, Clinical Affairs

1.0 BACKGROUND

The Sponsor is developing MSB11022 as a proposed biosimilar to US-licensed Humira and requested a BPD Type 4 meeting to discuss the content and format of the planned 351(k) BLA submission. Previous BPD Type 2 meeting responses and comments were issued March 16 and July 16, 2021.

The Sponsor's questions are noted in *italic* font below, followed by FDA's responses are in bold font and any Discussion between the Sponsor and FDA are in normal font. For the meeting the Sponsor requested to discuss Questions 1 a.1 and a. 3, Question 1b, Question 3 (2) (a).

FDA sent Preliminary Comments to the Sponsor on October 1, 2021.

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 the Sponsor and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

2.0 DISCUSSION

Question 1:
Does the Agency agree with the proposed clinical package to be included in the initial 351(k) BLA for MSB11022?

FDA Response to Question 1:
In your clinical package, you propose to include 3 studies: EMR200588-001; EMR200588-002; and FKS022-002. Your overall proposal is reasonable. You also propose to include studies EMR200588-003 and MS200588-004 as supportive clinical data. While submitting these supportive studies is at your discretion, we note that studies EMR200588-003 and MS200588-004 are not necessary to support the demonstration of biosimilarity between MSB11022 (C/Acetate) and US-licensed Humira.

We have the following additional comments about your studies:

a. *In the comprehensive discussion of clinical safety for Study EMR 200588-002 provide the following:*

   1) *Incidence rates for adverse events of special interest (AESIs: serious infections, including tuberculosis infection and opportunistic infections, new onset lupus-like syndrome, malignancy including lymphoma and leukemia and elevations in liver enzymes) by percent and adjusted for exposure in patient- years.*

   2) *Tabulations of treatment-emergent adverse events and adverse reactions with a ≥ 5% and ≥ 1% incidence.*

   3) *Subject narratives for all deaths, serious adverse events, adverse events of special interest, hypersensitivity reactions, adverse events resulting in discontinuation, and pregnancy regardless of the relationship to the study product. Include these narratives in Module 2.7.4 or provide electronic links. All associated case report forms (CRF) should be included in the submission or be available upon request.*

   4) *Line listings and shift tables for all laboratory values. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change, and your justification for why this threshold is appropriate.*

   5) *Tabulated summary of ECG results.*

b. *Note that our recommendations for the primary endpoint in a comparative clinical study in subjects with psoriasis have evolved since 2015. We now recommend evaluating the percent change in PASI at Week 16, evaluated using a 90% confidence interval with margins of ± 10. Thus, for Study EMR 200588-002, we recommend ensuring that the results for the percent change in PASI at Week 16 are included in your study report or in an addendum.*

c. *For each key clinical study, the Clinical Study Reports section should include the study report, all versions of the protocol, the statistical analysis plan, and an annotated case report form. Submit tabulation datasets (SDTM format) and analysis datasets (ADaM format preferred) in SAS transport format (.xpt). The analysis datasets should include all variables (including derived variables) needed for conducting the primary, secondary, and sensitivity analyses included in the study report. Include dataset documentation (define.xml) for tabulation and analysis datasets. The analysis dataset documentation should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables. Submit statistical programs for all complex or non-standard analyses.*

Discussion:

Refer to Slides 4, 5, 6

Question 1

a.1) The Sponsor provided a summary of their planned presentation of the protocol defined Adverse Events of Special Interest (AESI) in the Clinical Study Report (Serious Infections, Latent Tuberculosis (TB) and Active TB). The Sponsor proposed to submit tabulations and discussion of other AESI (e.g., new onset of Lupus-like syndrome, malignancies and liver enzyme elevations) in the 4-month safety update. The Agency indicated that in order to understand the safety-profile of MSB11022, the Sponsor needed to address/discuss the adverse events that are included in labeling for US-HUMIRA. The Agency agreed with the Sponsor's proposal to submit this information with the 4-month safety update.

Refer to Slides 7, 8

1 b) The Sponsor stated that the percent change in PASI at Week 16 endpoint was evaluated and analyzed in the clinical study report and provided a summary of which analysis are included in the report. The Sponsor noted that the 95% CIs included in the report for the difference between MSB11022 and EU-Humira fall within the margins of (-10%, 10%), for all analyses performed.

The Sponsor proposed submitting results using a 90% CI with the 4-month safety update.

The FDA responded that all that was needed was to submit a table with the calculations using the new confidence level and that they may just need to re-run their program with the 90% confidence level. FDA stated that it should be reasonable to include such a table as an addendum to the clinical study report in the initial submission vs. the safety update.

The Sponsor then made an alternative proposal to submit the results with the 90% CIs within 30 days of initial BLA submission. The FDA replied that they prefer that they be included in the initial submission however the very latest they may consider submitting the results is within 30 days from the date of initial submission.

Question 2:
The Company is planning to obtain approval for several packaging configurations in the original 351(k) BLA. The packaging configurations were developed in compliance with FDA draft guidance on safety considerations for carton labeling (FDA, 2013). The outer carton mockups for each packaging configuration is provided in Appendix 16.5. Does the agency have any comments on the Packaging configurations and mockups, and the HFS approach?

FDA Response to Question 2:
We do not have comments on your packaging configurations at this time. Your HF approach appears to be reasonable, however, we note that the review of your Threshold Analysis, Use Related Risk Analysis, and justification for not performing a Human Factors validation study for the 6-unit starter pack is ongoing. We will provide recommendations when our review is complete.

Discussion:
No further discussion was needed.

Question 3:
a. *Does the Agency have any feedback on the proposed structure and format of MSB11022 351(k) BLA as presented in Appendix 16.3 such that it meets the Agency's expectations for eCTD submission?*
b. *Does the Agency have additional comments on the adequacy of the proposed structure?*

FDA Response to Question 3a and 3b (combined):
The overall proposed structure and format of MSB11022 351(k) BLA as presented in Appendix 16.3 is reasonable. We have the following additional comments.

1. *For the comparative immunogenicity assessment, we recommend you provide brief summaries of the comparative immunogenicity results in Module 2.7 and the full report of Integrated Summary of Immunogenicity in Module 5.3.5.3. We refer you to the Guidance for Industry, Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection (https://www.fda.gov/media/119788/download), for detailed contents of the Integrated Summary of Immunogenicity.*
2. *For module 5, we recommend the following:*
   a. *In Module 5.3.6 Reports of post marketing experience provide a summary and a discussion of the safety findings to date with EU-approved Idacio in addition to the periodic benefit-risk evaluation reports (PBRERS).*
   b. *In Module 5.3.5.3 Reports of analysis of data from more than one study we recommend that you provide additional efficacy and safety analyses to support your comprehensive discussion of efficacy and safety in Modules 2.7.3 and 2.7.4. As previously communicated, tables and figures should be included in Section 5.3.5.3, along with appropriate explanation in both Modules 2 and 5.*

Discussion:

Refer to Slide 9

Question 3

2.a. The Sponsor provided a summary of their planned presentation of the periodic benefit-risk evaluation reports (PBRERs) to support the safety of MSB11022. Two PBRERs will be included in the initial marketing application in Section 5.3.6 and one PBRER with the 4-month safety update. The Sponsor will include a summary and discussion of the post marketing safety information with the 4-month safety update. The Agency agreed.

2.b. The Sponsor stated that a comprehensive summary and discussion of the safety findings will be provided in Section 2.7.4 Summary of Clinical Safety. The Agency agreed.

Question 4:

a. *Does the Agency have any feedback on the labeling concept for MSB11022 (Idacio) based on FDA Guidance for Industry – labeling for Biosimilar Products (July 2018), to support 351(k) BLA submission?*
b. *Does the Agency have any comments on the annotated draft USPI including medication guide for MSB11022?*

FDA Response to Question 4:

Your proposed labeling concept and draft USPI/Medication Guide are generally reasonable. Formal review of the proposed labeling will occur during the review cycle.

Discussion:

No further discussion was needed.

Question 5:

The Company is planning to provide only the revised PSP that was submitted to IND 124098 (Refer to eCTD Seq# 0050), in Module 1.9 of the BLA. Does the Agency have any comments on the approach?

FDA Response to Question 5:

Your proposed approach to include the indications protected by orphan exclusivity set to expire during the expected review cycle of the BLA submission for MSB11022 is reasonable.

We note that your March 31, 2021, submission includes the indications currently protected by orphan exclusivity, pediatric ulcerative colitis (UC) for patients 5 years of age and older, and adolescent hidradenitis suppurativa (HS) for patients 12 years of age and older. We acknowledge your proposal to include in the BLA submission a

pediatric assessment for the treatment of pediatric ulcerative colitis (UC) patients 5 years of age and older. While it is reasonable to submit this information in your BLA, we note that the Agency cannot license MSB11022 for this indication until the expiration of the exclusivity, and do not intend to make a formal determination or recommendation regarding licensure under section 351(k) for MSB11022 in pediatric UC.

Discussion:

No further discussion was needed.

Question 6:
MSB11022 is not the first adalimumab biosimilar to undergo Agency review and the Sponsor considers that no advisory committee meeting would be required for approval of the BLA. Does the Agency agree?

FDA Response to Question 6:
Although an advisory committee is not anticipated for this application, a final determination will be made after the BLA has been submitted.

Discussion:

No further discussion was needed.

Question 7a:
The Sponsor plans to submit specific manufacturing schedule options to support PAIs 6-8 months after BLA submission. The manufacturing schedule for MSB11022 DS and DP (PFS (b) (4) *will be aligned to support FDA PAI.*
Does the FDA agree that this schedule will meet the needs of the Agency for the PAI?

FDA Response to Question 7a:
Drug substance and drug product manufacturing schedules 6-8 months out from the time of BLA submission, provided they are included in the original submission, are acceptable.

Discussion:

No further discussion was needed.

Question 7b:
Does the FDA agree with the options provided below for the DP facility PAI?

FDA Response to Question 7b:
The options provided for the DP facility PAI appear to be acceptable.

Discussion:

No further discussion was needed.

Question 7c:
Can FDA comment on the potential impact of backlog on inspections caused by pandemic situation?

FDA Response to Question 7c:
We recently released the Resiliency Roadmap for FDA Inspectional Oversight that describes the systematic method for inspections and other oversight activities. The prioritization plan considers public health risks related to conducting an inspection, the impact of the product's availability on public health, as well as investigator safety and travel restrictions/advisories.

Also refer to guidances related to COVID-19, available at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

Discussion:

No further discussion was needed.

FDA Product Quality Microbiology comments

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

1. *All facilities should be registered with the FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.*

2. *Information and data for Chemistry, Manufacturing, and Controls (CMC) product quality microbiology should be submitted in the specified sections indicated below.*

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

1) *Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).*

2) *Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).*

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

4) *Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).*

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

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

7) *Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).*

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

   The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

   1) *Identification of the manufacturing areas and type of fill line (e.g., open, RABS, isolator), including area classifications.*

   2) *Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.*

   3) *Parameters for filling and plunger placement for the pre-filled syringes.*

4) *A list of all equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.*

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

6) *Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.*

c. *The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:*

1) *Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.*

2) *Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.*

3) *In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.*

4) *Isolator decontamination summary data and information, if applicable.*

5) *Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.*

6) *Information and summary results from shipping validation studies. For prefilled syringes/autoinjectors, the effects of varying air pressure on pre-filled syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the pre-filled syringe plunger movement during air transportation does not impact product sterility.*

d. *The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:*

1) *Container closure integrity testing. System integrity should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the pre-filled syringe and autoinjector should be included. Container closure integrity method validation should*

demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) until expiry.

2) *Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.*

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

4) *Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> Bacterial Endotoxin Test (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.*

Discussion:

No further discussion was needed.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The original 351(k) application will be subject to "the Program" under BsUFA II. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions regarding the approach to developing the content for risk evaluation and mitigation strategies (REMS), where applicable, patient labeling (e.g., Medication Guide and Instructions For Use) and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of

any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the BsUFA II agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on the Program is available at FDA.gov.[2]

PREA REQUIREMENTS

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

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

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive iPSP that addresses each indication. For additional information on how you may fulfill the requirement for pediatric assessments or investigations under PREA, see question and answer I.16 in the guidance for industry, *Questions and Answers on Biosimilar Development and the BPCI Act*.

[2] https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm

After the iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*[3]. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d)[4] and 201.57[5] 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[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

- 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.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended

[4] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

[5] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

[6] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm_084159.htm

[7] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.[8]

In addition, you should review the FDA guidance for industry *Labeling for Biosimilar Products* (July 2018).

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

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description

[8] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(k) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

MANUFACTURING FACILITIES

All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Manufacturing and testing facilities will be subject to the CGMP standards as described in 21 CFR 601.20, including but not limited to the good manufacturing practice requirements set forth in 21 CFR 210, 211, and 600 of this chapter.

Manufacturing facilities should be in operation and manufacturing the product under review during the inspection 2-7 months after the submission of the BLA. A manufacturing schedule for the drug substance and the drug product should be provided in Module 1 of the sBLA to facilitate planning of pre-license inspections during the review cycle. For when providing the preliminary manufacturing schedule, we encourage you to bear in mind the anticipated time frame for the late-cycle meeting for applications subject to "the Program" under BSUFA II.

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[9] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[10]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the

[9] https://www.fda.gov/media/84223/download
[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.

RECOMMENDATIONS FOR FORMATTING OF CLINICAL PHARMACOLOGY SUBMISSIONS FOR APPLICATIONS

If you are planning to include a clinical pharmacology study as part of your 351(k) BLA marketing application, we have the following general best practice recommendations for you to keep in mind as you prepare your submission, including guides for formatting your submission.

1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the 351(k) BLA:
    a. Include the rationale for the selected dose used in the PK (and PD similarity, when applicable) study(ies) in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
    b. Include a summary evaluation of the impact of immunogenicity on the activity (e.g., efficacy/PD), safety, and pharmacokinetics, as is applicable, for the studies included in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
    c. Present the PK (and PD, when applicable) parameter data as geometric mean with coefficient of variation, mean ± standard deviation, and median with range in the study reports and throughout the BLA.
    d. Provide analysis data sets for all concentration-time and derived PK (and PD, when applicable) parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
2. Include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
    a. Site number
    b. Principal investigator
    c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

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

3. Submit all PK (and PD, when applicable) bioanalytical method validation reports and bioanalytical study reports. In addition, complete the summary tables using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document[11] to provide the information regarding the bioanalytical methods for pharmacokinetic and/or biomarker assessments used in clinical pharmacology studies and their life-cycle information pertaining to the studies. Submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's slide deck

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

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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IND 124098

MEETING MINUTES

Fresenius Kabi SwissBioSim GmbH
[redacted] (b) (4)

[redacted]

[redacted] [redacted]

[redacted] [1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MSB11022.

We also refer to the meeting between representatives of your firm and the FDA on July 29, 2019. The purpose of the meeting was to discuss the assessment of the analytical similarity between MSB11022-acetate drug product and US-licensed Humira.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 3

Meeting Date and Time: July 29, 2019 at 3:00 PM
Meeting Location: FDA White Oak

Application Number: IND 124098
Product Name: MSB11022

Indication: MSB11022 is being developed for the same indications as approved for US-licensed Humira

Sponsor Name: Fresenius Kabi SwissBioSim GmbH
(b) (4)

Meeting Chair: Nikolay Nikolov, MD
Meeting Recorder: Jessica Lee, PharmD

FDA ATTENDEES

Nikolay Nikolov, MD, Associate Director for Rheumatology, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Juwaria Waheed, MD, Clinical Reviewer, DPARP
Jianmeng Chen, PhD, Acting Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Shalini Wickramaratne Senarath Yapa, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Cesar Torres, PhD, Biostatistics Reviewer, Division of Biometrics II, Office of Biostatistics
Kathleen Fritsch, PhD, Biostatistics Reviewer, Division of Biometrics III, Office of Biostatistics
Leslie Ann Rivera Rosado, PhD, Product Quality Team Lead, Office of Pharmaceutical Quality (OPQ), Office of Biotechnology Products (OBP), Division of Biotechnology Review and Research IV (DBRR IV)
Christopher Downey, PhD, Review Chief, OPQ, OBP, DBRR IV
Emanuela Lacana, PhD, Associate Director of Biosimilar & Regulatory Policy, OPQ, OBP
Stacey Ricci, M.Eng., Sc.D., Acting Director Scientific Review Staff, Office of Therapeutic Biologics and Biosimilars Staff
Michelle Luo, MD, PhD, Reviewer, Office of Therapeutic Biologics and Biosimilars
Cristina Ausin, PhD, Reviewer, Office of Therapeutic Biologics and Biosimilars Staff

Thomas Herndon, MD, Reviewer, Office of Therapeutic Biologics and Biosimilars Staff
Jessica Lee, PharmD, Senior Regulatory Project Manager, DPARP

SPONSOR ATTENDEES
Corinne Barra, Director Regulatory Affairs
Laurent Chevalet, Head of Analytical & Pharmaceutical Development
Zina Chir, Senior Biostatistician CMC
Kenrick Does, Head of Regulatory CMC
Laurent Magnenat, Head of Nonclinical Pharmacology
Georg Feger, SVP, Head of Research, Development, Manufacturing & Supply
Ina Frank, Head of Regulatory Affairs
Hilary Metcalfe, Head of Process Development & Manufacturing Sciences
Joelle Monnet, Director Biostatistics
Fabrice Romanet, VP Program Leadership, Regulatory and Governmental Affairs
Martin Ullmann, Head of Bioanalytics
Barbara Valenta-Singer, Chief Medical Officer
Seema Kumbhat, SVP, Regional Medical Director

1.0 BACKGROUND

In a submission dated April 2, 2019, the Sponsor requested a meeting to discuss the assessment of the analytical similarity between MSB11022-acetate drug product and US-licensed Humira. The meeting was granted on April 10, 2019. The Sponsor's questions from the briefing package dated April 2, 2019 are listed below in *italics font*, and FDA responses and meeting Discussions are provided in normal font.

FDA sent Preliminary Comments to Fresenius Kabi on July 25, 2019. Fresenius Kabi provided slides with discussion points for the meeting on July 29, 2019 (see Section 6.0 below).

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 Fresenius Kabi 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 FDA agree that the proposed criticality risk ranking of the quality attributes are appropriate for the assessment of analytical similarity of MSB11022 to the US-RP?

FDA Response to Question 1:

Yes, the criticality risk ranking of the quality attributes appears acceptable. Refer to our response to Question 2 below.

Discussion to Question 1:

No discussion.

Question 2:

Does the FDA agree with the proposed assignment of tiers for the statistical analysis of data from the physicochemical and biological test methods and with the justification of the X SD multiplier for Tier 2 attributes?

FDA Response to Question 2:

In regard to analytical data evaluation, we refer you to the May 2019 Draft Guidance for Industry- *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (https://www.fda.gov/regulatory-information/search-fda-guidancedocuments/developmenttherapeutic-protein-biosimilars-comparative-analytical-assessment-and-other-quality) for the Agency's current recommendations on the design and evaluation of comparative analytical studies intended to support a demonstration that a proposed therapeutic protein product is biosimilar to a reference product licensed under section 351(a) of the Public Health Service Act (PHS Act).

If you intend to continue with your proposed statistical approach, in general terms, we agree with the statistical methods you propose to use for the comparative analytical assessment of "very high, high, and moderate risk" attributes (i.e., equivalence testing and assessment by quality range), and "low risk" attributes (i.e., graphical representations and summary statistics tables). However, we do not agree at this time with your proposal to use 3 as a multiplier (X = 3) for the assessment of some "very high" and "high"-risk quality attributes (e.g., binding to soluble TNF). To analyze data for some "very high, high, and moderate" risk attributes, you proposed to set quality ranges as the mean of US-licensed Humira batches tested using a multiplier of ± 3 standard deviations. To justify your approach, you stated that "X = 3 is widely accepted in the pharmaceutical industry as a reasonable range based on the variability in the reference product, and a similar product would be expected to pass the criterion." The standard deviation multiplier should be scientifically justified for each specific test measure (or quality attribute), taking into account not only the variability of the reference product and of the assay, but also the nature and the potential impact of each individual attribute on the mechanism of action of the product. Note that the Agency recommends that narrower acceptance criteria of the quality range method in comparative analytical assessment (e.g., a lower X value) be applied to higher risk quality attributes. For attributes with lower risk ranking, or

for attributes that cannot be quantitatively measured, the Agency recommends side-by-side data presentation (e.g., spectra, thermograms, graphical representation of data), to allow for comparison of MSB11022 to US-licensed Humira.

Discussion to Question 2:

The sponsor plans to provide a comparative analytical assessment that includes (1) a minimum of 14 MSB11022 batches from Process A and a minimum of 6 MSB11022 batches from Process C, (2) comparative stress testing of MSB11022 Process C, MSB11022 Process A and US-licensed Humira, and (3) comparative fractionation/ characterization of variants from MSB11022 Process C vs US-licensed Humira. Additionally, the sponsor provided examples of graphical and tabulated data presentations of the planned statistical tiers as presented in slides 5-9; refer to Section 6.0.

Overall, the Agency found the proposed comparative analytical assessment plan acceptable; however, the Agency stated that to support the scientific bridge to US-licensed Humira, the sponsor should also include EU-approved Humira in the comparative analytical assessment, comparative stress testing, and the comparative characterization of variants. Regarding the presentation of data (slides 5 – 7), the Agency recommended that the data be color coded to distinguish data points derived from Processes A and C in the graph for clarity.

In support of the scientific bridge for attributes assigned to “Tier 1, 2, and 3,” the Agency reiterated that data from EU-approved Humira batches should be included in all comparative analytical assessments and that all pairwise comparisons of the scientific bridge should be evaluated using the same statistical methodology used for the evaluation of analytical similarity between MBS11022 and US-licensed Humira. For example, slide 5 proposes comparing MSB11022 potency by cell-based assay to US-licensed Humira and to EU-approved Humira by statistical equivalence testing (“Tier 1”); EU- approved Humira should be compared to US-licensed Humira by the same statistical methodology to support establishing the analytical portion of the scientific bridge.

It was discussed that for qualitative data (“Tier 3”) it is best to include all the available data. The Agency agreed with the sponsor’s proposal to include data from three representative batches of each product, including process A and EU-approved Humira data (if available) for qualitative attributes. The Agency notes that Fresenius will need to provide scientific rationale for all lots selected for inclusion in the comparative analytical assessment.

Question 3:

Does the FDA agree with the Applicant’s bridging strategy? Specifically:

a) *Following the FDA's advice, the Applicant adjusted the manufacturing process of MSB11022, and performed extensive analytical comparability and similarity assessments to comprehensively evaluate the impact of the process adjustments on the similarity of MSB11022-acetate Process C with the US-RP. Does the FDA agree that this approach and the data generated are appropriate to support a highly similar analytical profile?*

b) *Following the FDA's advice, the Applicant proposes to perform a clinical study to compare the PK, safety, and immunogenicity profiles of MSB11022-acetate Process C with both the USRP and EU-RMP. Does the FDA agree that this approach is appropriate and sufficient to provide the necessary bridge to the existing body of clinical data to support the demonstration of a highly similar clinical profile?*

c) *Is the proposed approach and intended data package contributing to the totality of analytical and clinical similarity evidence appropriate and sufficient to support licensure for MSB11022-acetate Process C as a biosimilar to the US-RP?*

FDA Response to Question 3a:

We agree that based on the limited comparative analytical assessment data provided in the meeting package, MSB11022 lots manufactured using Process C have profiles that more closely match the quality attributes of US-licensed Humira, including afucosylated glycans levels and in vitro ADCC activity, than lots manufactured using Process A. However, final evaluation of the comparative analytical assessment data is a review issue and will be assessed during the review of your 351(k) BLA application. Additionally, refer to our response to Question 2.

FDA Response to Question 3b) and 3c):

You are proposing to conduct Study FKS022-002, which is a "Phase I", randomized, double-blind, parallel-group, 3-arm, single-dose study designed to compare the PK, safety, tolerability, and immunogenicity of MSB11022-acetate Process C with US-Humira and EU-Humira in healthy subjects. At a minimum, we believe that you need to generate comparative PK and immunogenicity data for the proposed commercial product and US-licensed Humira. You also need to establish adequate analytical and PK comparability between the MSB11022-acetate Process C and the MSB11022 Process A product to justify the relevance of the data generated with the MSB11022 Process A drug product to support a demonstration of biosimilarity between MSB11022-acetate Process C and US-licensed Humira. This may include data from study EMR200588-001—which could provide the data for the necessary bridge between EU-Humira and US-Humira—as well as the comparative clinical study in subjects with PsO (EMR200588-002).

The proposed study FKS022-002 would not be adequate to justify reliance on data generated with the MSB11022 Process A drug product to support a demonstration of

biosimilarity for MSB11022. We recommend that, in addition to collecting the analytical data discussed in the FDA responses to Questions 1, 2, and 3a, you should also establish PK comparability between the MSB11022-acetate Process C formulation and the MSB11022-citrate Process A formulation. Further, you should include US-Humira as the 3rd arm of the PK study to compare PK and immunogenicity between MSB11022-Acetate C and US-Humira. Therefore, we recommend you conduct a 3-way PK similarity study between MSB11022-acetate Process C, MSB11022-citrate Process A, and US-Humira. The adequacy of the data to support a demonstration of biosimilarity will be a review issue.

Discussion to Question 3:

The sponsor provided a revised design for their proposed PK bridging study; refer to slides 12 and 13 in Section 6.0. For the proposed PK bridging study, the sponsor stated that a MSB11022-citrate Process A vs. US-licensed Humira comparison was not planned since this comparison was already done in the completed PK similarity study (EMR200588-001). The Agency acknowledged this previous comparison, and recommended that the primary objectives of the study should be to demonstrate PK similarity between MSB11022-acetate Process C and US-licensed Humira and between MSB11022-acetate Process C and MSB11022-citrate Process A. The secondary objective of the study should be to demonstrate PK similarity between MSB11022-citrate Process A and US-licensed Humira. The Agency also recommended that the planned study should be powered to demonstrate PK similarity between MSB11022-citrate Process A and US-licensed Humira.

Discussion to Question 3b) and 3c):

The sponsor provided the clinical studies that will be included in the BLA application; refer to slides 15-16 in Section 6.0.

The sponsor proposed that an integrated summary of efficacy (ISE) will not be provided as it would be inappropriate to pool efficacy data across indications (Psoriasis, Healthy Volunteers (HV), and Rheumatoid Arthritis (RA)).

Similarly, the sponsor proposed that an integrated summary of safety (ISS) will not be provided due to the difference in study populations (Psoriasis, HV and RA), and also because of concomitant MTX use in RA (but not in Psoriasis or HV studies).

Instead, the sponsor proposed efficacy and safety results will be presented in the Clinical Overview and in the respective sections of Summary of Clinical Efficacy and Summary of Clinical Safety.

The Agency found the sponsor's proposal reasonable given the different patient populations. 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 are required by the regulations, and would be located in Module 5. However, if the sponsor believes 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 the sponsor may place the summary portion of the integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in section 5.3. In this case, an explanation should be placed in both Module 2 and Module 5.

Lastly, it was discussed that BIMO listings should be provided for all comparative clinical studies that are necessary to support a demonstration of biosimilarity for MSB11022.

Question 4:

Does the FDA agree with the Applicant's proposed study design for the suggested bridging Study FKS022-002, specifically with reference to the:

- *Study population.*
- *Dose.*
- *PK endpoints ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max}) and PK similarity criteria.*
- *Sampling duration.*
- *Sample size and study power.*
- *Assessment of immunogenicity and safety.*

FDA Response to Question 4:

Refer to the FDA Response to Question 3b) and 3c).

If you revise Study FKS022-002 to address the FDA responses to Question 3b) and 3c) regarding the products that should be evaluated, in general, the study population, dose, PK endpoints and PK similarity criteria, and sampling duration appear reasonable.

For sample size calculation, we agree that the PK similarity margin of 0.8-1.25 is reasonable, and we agree on the 90% CI for the ratio of geometric means of test/reference for the PK parameters and your planned power (at least 80%). The other aspects of sample size calculation, such as assumption of the coefficient of variation, the ratio of geometric means between test product and reference product, and the drop-out rate are at your discretion.

Descriptive assessment of immunogenicity and safety in the PK similarity study are expected.

Discussion to Question 4:

The sponsor proposed a descriptive assessment of immunogenicity by evaluating the incidence and titer of ADAs and incidence of NAbs in response to the single dose treatment in healthy subjects, which the Agency found reasonable and had no additional comments.

Additional CMC comments:

Following binding to mTNF-α, adalimumab may mediate a range of biological responses including antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). Thus, both ADCC and CDC, through a Fc-domain-dependent mechanism, are potential mechanisms of action of the product. Develop and implement a comprehensive and robust control strategy to control for these effector functions of MSB11022 and provide justification to support your proposal in your 351(k) BLA submission.

Discussion of Additional CMC comments:

The Agency stated that the correlation described by the sponsor between afucosylation and ADCC and galactosylation and CDC may not represent the only factors affecting these effector functions. The Agency recommended that assays that are more closely related to the in-vivo activity should be part of the release specifications, for example, cell-based assays or binding to the relevant receptors. If receptor binding is to be used, then the sponsor should provide data showing the correlation between receptor binding and in-vivo activity.

(b) (4)

3.0 OTHER INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Please be advised that an original 351(k) BLA will be subject to "the Program" under BsUFA II. Therefore, at an appropriate time, you should request a BPD Type 4 (pre-351(k) BLA) meeting and be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions regarding the approach to developing the content for risk evaluation and mitigation strategies (REMS), where applicable, patient labeling (e.g., Medication Guide and Instructions For Use) and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components

of the application are expected to be included in the original application and are not subject to agreement for late submission.

Include in your BPD Type 4 meeting package your proposals for 1) the content of a complete application and 2) any minor components to be submitted within 30 days after your original submission. You should also include, as part of your meeting questions, a request for our agreement with your proposals.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

PREA REQUIREMENTS

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

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

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a

[2] https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm

comprehensive iPSP 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.16 in FDA's draft guidance for industry on New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) (December 2018). 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 iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *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. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

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.[3]

On December 17, 2014, FDA issued final guidance *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*. 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,[4] 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 started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December

[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[4] http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

17, 2017. CDER has produced a Study Data Standards Resources web page[5] 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 started on or 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.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[6] The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30)[7] includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[8] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[9]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[6] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm
[7] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[9] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website found at FDA.gov.[11]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[12]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[13]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Refer to Sponsor's meeting slides.

[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf
[12] http://www.fda.gov/ectd
[13] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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JESSICA K LEE
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