CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761275Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 129965

MEETING PRELIMINARY COMMENTS

Fresenius Kabi SwissBiosim GmbH
c/o Fresenius Kabi USA LLC
801 Pennsylvania Ave NW #820
Washington DC 20004

Attention: Navayath Shobana, PhD
Director, Global Regulatory Affairs

Dear Dr. Shobana:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MSB11456.

We also refer to your correspondence, dated and received January 28, 2022, requesting a meeting to discuss the planned 351(k) BLA submission for MSB11456.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call me at (240) 402-2925.

Sincerely,

{See appended electronic signature page}

Susie Choi, PharmD
Regulatory Project Manager
Rheumatology and Transplant Medicine
Division of Regulatory Operations -
Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: March 29, 2022, 12:00-1:00 PM ET
Meeting Location: Teleconference

Application Number: 129965
Product Name: MSB11456
Indication: MSB11456 is being developed for the same indications as approved for US-licensed Actemra

Sponsor Name: Fresenius Kabi SwissBiosim GmbH c/o Fresenius Kabi USA
Regulatory Pathway: 351(k) of the Public Health Service Act

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 29, 2022, between Fresenius Kabi USA and the Division of Rheumatology and Transplant Medicine. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Fresenius Kabi SwissBiosim GmbH (Fresenius Kabi) submitted a BPD Type 4 meeting request on January 28, 2022, to discuss their planned 351(k) BLA submission for MSB11456, a proposed biosimilar to US-licensed Actemra (tocilizumab). A teleconference was granted on February 18, 2022. Fresenius Kabi's questions from the briefing package, dated January 28, 2022, are provided in italics, followed by FDA responses in normal font.

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

2.0 DISCUSSION

Question 1

(a) Does the FDA agree that providing tentative manufacturing schedule in the iBLA will meet the needs of the Agency and that the exact schedule can be confirmed closer to the PAI time?

(b) Can FDA comment on the potential impact of backlog on inspections caused by the pandemic situation?

FDA Response to Question 1:

Thank you for committing to provide in the initial BLA tentative manufacturing schedule options to support Pre-approval inspection (PAI) 6-8 months after initial BLA submission. The information will be considered during our assessment of the facilities and planning the inspection(s), as needed. The facilities listed in each submission are evaluated using a risk-based approach. We will use all available tools and sources of information to support regulatory decisions on submitted applications including those with manufacturing sites impacted by travel restriction due to the COVID-19 pandemic. The tools may include an evaluation of a firm's previous compliance history, use of information from trusted foreign regulatory partners through mutual recognition agreement and other confidentiality agreements, requesting records "in advance or in lieu of" facility inspections or voluntarily from facilities and sites and conducting remote interactive evaluation, where appropriate, as described in "Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency".

In some cases, these alternative tools may not provide sufficient information to mitigate the need for an inspection. Please refer to the guidance "Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency, Question and Answers May 2021 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-supply-chain-and-drug-and-biological-product-inspections-during-covid-19-public-health) for further information on inspections.

As travel restrictions are eased or lifted, FDA will use a risk-based approach to prioritized inspections. The prioritization strategy will consider the impact of product availability on public health; investigator safety; and travel restrictions still in place during the COVID-19 public health emergency. These considerations will be balanced with the goal to reduce any backlog of assigned inspections. Please refer to FDA's "An Update to the Resiliency Roadmap for FDA Inspectional Oversight", November 2021 (https://www.fda.gov/media/154293/download) for further information on FDA's prioritization plan for the inspectional oversight activities.

For more information, refer to FDA guidances related to COVID-19. These guidances can be found 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.

Question 2:
The Company proposes to submit the shipping validation data for one batch each of PFS auto-injector and (b) (4) combination products in the initial BLA, and the additional shipping validation data for three batches each (thereby implementing FDA feedback dated 30 June 2021) at the time of the 4 months safety update. Does the Agency agree?

FDA Response to Question 2:
Your proposal to submit the real time and simulated shipping validation studies for MSB11456 in auto-injector (AI) and in (b) (4) (PFS (b) (4)), using one batch of drug product assembled with one batch of device in the final to-be-commercialized packaging in the initial BLA followed by additional simulated and real time shipping validation testing on 3 batches of mid aged drug product (DP) and 3 batches of end of shelf-life aged devices with the final commercial product packaging, is acceptable.

Question 3:
The Company proposes the date of the BLA submission to be the cut-off for the 4-month safety update. Does the Agency concur?

FDA Response to Question 3:
You propose that the 4-month safety update report will provide a summary update of all new safety data gathered since the data cut-off for the BLA submission documents (Study FKS456-001 Week 30 CSR cut-off date in October 2021) to the date of the BLA submission (estimated May 2022). This proposal is reasonable.

Question 4:
Does the FDA have any feedback or recommendations regarding the proposed content and format of MSB11456 351(k) BLA as presented in Table of Contents?

FDA Response to Question 4:
Your plan to submit Human Factor (HF) results as part of your marketing application appears reasonable. Please refer to our draft Guidance for Industry and FDA Staff, entitled, "*Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*"[1] for the content of a human factors validation study report submission. Human Factors study results should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

[1] https://www.fda.gov/media/122971/download

Question 5
Does the Agency agree or have any feedback on the Sponsor's approach to demonstrate compliance with 21 CFR 312.120 for the comparative PK non-IND Study MS200740-0001?

FDA Response to Question 5:
Your approach to demonstrate compliance with 21 CFR 312.120 appears reasonable; whether your justification and information provided to satisfy 21 CFR 312.120 is acceptable will be considered in review of your application. We refer you to the Guidance for Industry and FDA Staff, "*FDA acceptance of Foreign Clinical Studies not conducted under IND: Frequently asked questions*," which provides detailed information regarding documentation which must be provided with your application. The guidance is available at FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions | FDA.

Question 6:
Does the Agency concur that the currently agreed Initial Pediatric Study Plan without any further amendments would be acceptable for the purpose of the BLA submission?

FDA Response to Question 6:
We agree.

Question 7:
Can the Agency advise on the choice of differentiating elements including colors between the 3 presentations (PFS, AI, vial) and strengths proposed for MSB11456?

FDA Response to Question 7:
The assessment of label, labeling, and packaging design are review issues. A review of the proposed label, labeling and packaging design will be conducted once the application is submitted; we will provide detailed comments and recommendations at that time.

Question 8:
Does the Agency have any feedback on the labeling concept and content for MSB11456 based on FDA Guidance for Industry – Labeling for Biosimilar Products (July 2018), to support 351(k) BLA submission?

FDA Response to Question 8:
In general, your overview of the labeling concept for MSB11456 as provided in Table 21 of your briefing package appears reasonable; however, assessment of labeling will be a review issue.

Question 9:
Would FDA consider the possibility of Priority Review for the MSB11456 351(k) BLA in view of the challenging supply situation of tocilizumab in the ongoing pandemic situation?

FDA Response to Question 9:
The eligibility for a Priority Review designation is determined once the BLA has been submitted. As you noted, Priority Review designation is considered based on evidence suggesting the potential for a product to provide a significant improvement in safety or effectiveness for a specific serious or life-threatening condition. Please refer to the Guidance for Industry, *Expedited Programs for Serious Conditions – Drugs and Biologics,* available at https://www.fda.gov/media/86377/download.

FDA ADDITIONAL COMMENTS

Product Quality:

(b) (4)

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

3.0 OTHER IMPORTANT MEETING LANGUAGE SECTIONS

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.

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.

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

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*.

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

[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

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
- 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.

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[6] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

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

[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.

NONPROPRIETARY NAME

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 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.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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 BLA to facilitate planning of pre-license inspections during the review cycle. For a BLA submission, 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 and the guidance for industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers . 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 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[9] 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.

[9] 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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