CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761154Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 116471

MEETING MINUTES

Fujifilm Kyowa Kirin Biologics Company
(b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for FKB327.

We also refer to the meeting between representatives of your firm and the FDA on January 13, 2017. The purpose of the meeting was to seek feedback and agreement on your proposed structure, format, and content of FKB327, a proposed biosimilar to US-licensed Humira.

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

If you have any questions, call me at (301) 796-2777.

Sincerely,
{See appended electronic signature page}
Sadaf Nabavian, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center of Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Biosimilar
Meeting Category:	Biosimilar Biological Product Development (BPD) Type 4
Meeting Date and Time:	January 13, 2017; 1:00-2:00 P.M. EST
Meeting Location:	Building 22, Conference Room 1419
Application Number:	IND 116471
Product Name:	FKB327
Indication:	FKB327 is being developed for the same indications as approved for US-licensed Humira
Sponsor:	Fujifilm Kyowa Kirin Biologics (FKB) Co., Ltd. Company [redacted] (b) (4) (U.S. Agent)
Meeting Chair:	Badrul A. Chowdhury, MD, PhD
Meeting Recorder:	Sadaf Nabavian, PharmD

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Nikolay Nikolov, MD, Clinical Team Leader, DPARP
Keith Hull, MD, PhD, Clinical Reviewer, DPARP
Anshu Marathe, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Renu Singh, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Gregory Levin, PhD, Statistical Team Leader, OTS/OB/DBVII (via phone)
Timothy Robison, PhD, Pharmacology/Toxicology Team Leader, DPARP
Matthew Whittaker, PhD, Pharmacology/Toxicology Reviewer, DPARP
Juhong Liu, PhD, Review Chief, Office of Pharmaceutical Quality (OPQ), Office of Biotechnology Products (OBP), Division of Biotechnology Review and Research II (DBRRII)
Tim Wadkins, PhD, Product Reviewer, OPQ/OBP/ DBRRII
Sue Lim, MD, Medical Officer Team Leader, Office of New Drugs (OND), Therapeutic Biologics and Biosimilars Staff (TBBS)
Stacey Ricci, MEng, ScD, Senior Toxicologist, OND, TBBS
Leila Hann, Science Policy Analyst, OND, TBBS (via phone)
Tyree Newman, Sr. Regulatory Health Project Manager, OND, TBBS (via phone)
Mishale Mistry, PharmD, MPH, Team Leader, Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management (OMEPRM), Office of Surveillance and Epidemiology (OSE),
Carlos Mena-Grillasca, RPh, Safety Evaluator, DMEPA, OMEPRM, OSE

Daniel Orr, MA, JD, Regulatory Counsel, Office of Regulatory Policy, Division of Regulatory Policy
Elizabeth Daugherty, Pharmacy Intern, University of Georgia
Marion Michaelis, Consumer Safety Officer, DIA, FDA
Lening Shen, General Engineer, CDRH/ODE/DAGRID/GHDB/FDA
Emily Jing, Biologist, OBP, FDA
Lindsey Brown, PhD, Microbiologist, DMA, FDA
Candace Gomez-Broughton, PhD, Microbiologist, DMA, FDA
Yongmin Liu, PhD, CMC Reviewer, OBP, FDA
Maxwell Van Tassell, PhD, Microbiologist, OPF, DMA, FDA
Zhuang Miao, PhD, Statistical Reviewer, OB, FDA
Tim Wadkins, PhD, CMC Reviewer, OBP, DBRR2, FDA
Patricia Love, MD, Deputy Director, Office of Combination Products, OSMP, FDA
Sadaf Nabavian, PharmD, Sr. Regulatory Project Manager, DPARP

SPONSOR ATTENDEES
Yasumasa Arai, General Manager of Clinical Department
Keiichiro Matsusaka, General Manager of Pharmacovigilance Department
Takafumi Iura, Senior Scientist of Analysis Technology Development Group, Production & Development Center
Tetsuji Hayashi, Senior Scientist of R&D Planning Administration Group, Bio Process Research and Development Laboratories, Production Division
Wataru Kurihashi, Senior Scientist of Formulation Development Group, Production & Development Center
Ryosuke Endo, Senior Scientist of Formulation Development Group, Production & Development Center
(b) (4) Principal Consultant, VP, Early Stage Development
Gary Trewartha, Senior Manager of Regulatory Affairs Department
Toshihiro Izawa, Regulatory Affair Department
Hideaki Nomura, Presdident and CEO (via phone)
(b) (4) Consultant (via phone)
(b) (4) President and Principal Consultant
(b) (4) Consultant

1.0 BACKGROUND

Fujifilm Kyowa Kirin Biologics (FKB) Co., Ltd. Company/(b) (4) (U.S. Agent) submitted a BPD Type 4 Meeting Request to seek advice feedback and agreement on their proposed structure, format, and content of a biologics license application (BLA) to be submitted under section 351(k) of the Public Health Service Act (PHS Act) for FKB327, a proposed biosimilar to US-licensed Humira (adalimumab). The FDA's preliminary comments were sent to Fujifilm Kyowa Kirin Biologics (FKB) Co., Ltd. Company/(b) (4) (U.S. Agent) on January 12, 2017. After review of these comments, Fujifilm Kyowa Kirin Biologics (FKB) Co., Ltd. Company/(b) (4) (U.S. Agent) stated their intent to continue with the meeting as scheduled and requested to discuss the FDA's responses to Questions 5, 6, 7, 14, 15, 17, 19, 25, and 26. Fujifilm Kyowa Kirin Biologics (FKB) Co., Ltd. Company/(b) (4) (U.S. Agent) also provided the responses/discussion points via email to Ms. Sadaf

Nabavian prior to the meeting (also in ***bold italic***) and incorporated before the discussion sections for ease of follow.

The questions from Fujifilm Kyowa Kirin Biologics (FKB) Co., Ltd. Company/ (b) (4) (U.S. Agent) are in bold italic, FDA's responses to the questions are in italic, and any discussion that took place between Fujifilm Kyowa Kirin Biologics (FKB) Co., Ltd. Company/ (b) (4) (U.S. Agent) and the FDA are in regular font.

FDA may provide further clarifications of, or refinements and/or changes to the responses and the advice provided at the meeting based on further information provided by Fujifilm Kyowa Kirin Biologics (FKB) Co., Ltd. Company/ (b) (4) (U.S. Agent) and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the PHS Act.

2. DISCUSSION

Question 1:
The BLA will be submitted in Common Technical Document (CTD) format through the Electronic Submissions Gateway. The content of the BLA is based on FDA regulations and Guidelines. The BLA is considered to be complete. Does the FDA agree? If not, what additional information and/or data need to be submitted?

FDA Response:

In general your proposal appears reasonable. However, also refer to the FDA responses throughout this document for additional guidance on the information needed to support your future BLA submission. Whether your application is complete will be determined during our filing review.

Discussion:

No discussion took place.

Question 2:
The modules of the BLA have been organized according to FDA Guidelines and advice. Does FDA agree that the organization is acceptable for the review of the BLA? If not, how should the organization be changed?

FDA Response:

The organization of the modules appears to be acceptable; additional information is included in the additional microbiology comments.

From a technical standpoint (not content related) yes, the proposed organization for the planned BLA is acceptable. However, see our additional comments below:

- *M1.6.3 Correspondence regarding meetings – a single pdf file of all meeting documents can be provided (instead of individual pdf files) with proper bookmarks, table of contents and hyperlinks.*

- *For archival purposes, also submit a pdf file of any document submitted in word. When you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.*

- *Providing Table of Contents in 2.1 and 4.1 is not necessary in the eCTD structure. However, the proposed reviewer's guide will be helpful.*

- *Providing a single 2.3.P for "PFS" Product and differentiating documents by leaf title (e.g. Stability-20mg PFS, Stability-40mg PFS, etc.,), is acceptable*

- *Do not create additional nodes in m2.3.p and m3.2.p (e.g. m2.4.1, m2.5.1, etc.,) in the eCTD structure beyond what is in the specifications. Make sure your approach fits the DTD and the "Granularity Annex", located at:- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf*

- *The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be linked to the referenced studies in m5.*

- *Do not provide section numbers in m4 and m5 heading nodes (e.g. m4.2.1.1.1, 4.2.1.1.2, m5.3.1.2.1, 5.3.1.4.1, etc.,).*

- *Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF, including case report forms (crfs). Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located here:- http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf*

- *Regarding use of the m5-3-7 heading element, FDA does not use module 5.3.7 CRFs. Instead, case report forms need to be referenced under the appropriate study's STF, organized by site as per the specifications and tagged as "case report form". Do not use m5.3.7 as a heading element in the index.xml.*

- *Include "HF" in the leaf titles of the Human Factor files so reviewers can easily identify the documents.*

- *For additional information on where to provide device constituent part information using the eCTD format please see eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD*

Specifications" http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf. (September 2016)

Discussion:

No discussion took place.

Question 3:

Information and data already submitted in electronic format with the eCTD backbone files will not be submitted again. Instead, the information will be included by reference. A document placed in the appropriate CTD section of the already submitted document will contain (1) the application and amendment number, (2) the date of submission and (3) the document name of the referenced document. A hypertext link to the location of the information will also be included. If a document replaces or appends a document previously submitted, these documents will be included in the BLA. Does FDA agree with this approach?

FDA Response:

No, we do not agree. Submit all the information in your future BLA submission.

Also, letters of Authorization from DMF holders should be listed in Module 1.4.2. Pyrogen Study Reports should be listed in Module 3.2.P.3.5.

Refer to additional microbiology comments for organization of data.

Discussion:

No discussion took place.

Question 4:

The Biologics Price Competition and Innovation Act contains patent provisions. As such, should patent information be included in Module 1.3.5.1? If yes, please provide advice on what information the Agency requires in this section.

FDA Response:

Section 351(l) of the PHS Act, as amended by the BPCI Act, describes certain procedures for information exchanges and the resolution of patent rights between a biosimilar applicant and the reference product sponsor after a biosimilar application is filed under section 351(k). These procedures are parallel to, but separate from, the FDA review process. The BPCI Act generally does not describe any FDA involvement in monitoring or enforcing the information exchange. Patents are not required to be listed in a 351(k) application.

Discussion:

No discussion took place.

Question 5:
Manufacture of FKB327 takes place in Japan. Production and testing staff follow procedures written in the local language (Japanese). The BLA will contain accurate and complete English translations of all parts of the application; however, a template Batch Production Record in English will be included in the BLA to enable the review of the executed Batch Production Records which are in Japanese. In addition, Analytical Method Validation reports will be submitted in Japanese and translated into English. Does the Agency find this approach to be acceptable and thus, will not be a reason to Refuse to File the BLA?

FDA Response:

Your approach is acceptable. However, to facilitate our review, submit only the English translation of the following in your BLA:

1) *Executed Batch Production Records for one of the process validation batches.*
2) *Analytical method validation reports.*

Summary data and qualification report of compendial microbiology methods in English should be included in the BLA.

FKB's Response:

- ***Given FDA confirmed in the written comments that FKB's proposed approach was acceptable, FKB would like FDA to confirm if the proposal to provide the following is acceptable:***

  -Provision of the master batch record in English and the executed batch record with operator comments and results in Japanese.

Discussion:

The FDA accepted FKB's proposal. The FDA requested English translations of the following:

-Executed batch production records for one of the process validation batches
-Analytical method validation report
-Summary data and qualification report of compendial microbiology methods

The FDA accepted FKB's proposal that includes provisions of the master batch record from the process validation batch translated to English and executed batch record with operator's comments and results in Japanese.

Question 6:
Analytical methods for control testing will be described in sufficient detail in accordance with FDA Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics (July 2015). The title and internal identification number of Standard Operating

Procedures (SOPs) for control of drug substance/drug product, and their stability, will be provided in the BLA; however, no written procedure, that is, no SOPs, will be included in the BLA. Will this strategy permit a timely, efficient, and complete review of the BLA?

FDA Response:

Yes, your strategy is acceptable. However, we may request relevant translated SOPs during the review cycle.

Detailed descriptions of compendial microbiological methods in English should be included in the BLA.

FKB Response:

- ***FKB had not planned on providing detailed descriptions of the compendial microbiological methods in the BLA as all methods are conducted exactly in accordance with the USP monographs.***
- ***Can FDA provide further information on why detailed descriptions of compendial methods are required?***

Discussion:

FKB stated that the compendial microbiology methods included in Modules 3.2.S.4.2 and 3.2.P.5.2 were in compliance with USP and sought clarification in FDA's request. FDA replied that they recommend that a brief description of the compendial methods with a summary of the qualification data should be included in the BLA.

Question 7:
Raw data results for multiple proposed biosimilar lots and reference product lots obtained during the analytical and functional similarity exercise will be provided as figures in the BLA to facilitate FDA review of similarity. Does the Agency consider this approach to be acceptable?

FDA Response:

No, we do not agree that raw data will be provided as figures only. To facilitate the review of the statistical analyses, in addition to figures, also submit numerical results that generated each figure in table format. Submit a table and an accompanying figure for each attribute measured by a quantitative method included in your analytical similarity assessment.

FKB's Response:

FKB confirms that in addition to the representative figures, tabulated results for each method conducted during the similarity exercise are included in the biosimilarity section (PDF format) in the Module 3 document.

Does FDA confirm that this is acceptable?

Discussion:

The FDA stated that the proposed format is acceptable but clarified that FKB should also include the tabulated results for each for Tier 1 and 2 attribute, and for Tier 3 attributes as appropriate. The FDA also clarified that the figures provided should not be representative, but rather should include the results for each attribute for all FKB327 and the reference product lots used in the similarity assessment. FKB replied that they will include the requested information in Module 3.

Question 8:
For drug substance and product manufacturing sites, facility and equipment information as described in Guidance for Industry M4Q: The CTD – Quality (August 2001) will be included in the BLA. Does the Agency find this to be acceptable?

FDA Response:

Yes, your proposal is acceptable and in line with the Guidance for Industry M4Q: The CTD – Quality (August 2001) requirements to be submitted with your BLA. Descriptions of sterilization and depyrogenation of equipment in contact with sterile product should be listed in Module P.3.3. Summary validation data and information for the sterilization and depyrogenation process of sterile product contact equipment should be included in Module P.3.5.

Additional information on the facility and equipment should be available at the manufacturing sites for review during the pre-license inspection(s).

Discussion:

No discussion took place.

Question 9:
In vivo nonclinical reports for studies using EU-approved Humira® as the reference product have been submitted to the IND (original IND 0000). As the reference product for the FKB327 comparative clinical study was US-licensed Humira® and the original IND included human clinical data from the Phase 1 PK study, these nonclinical studies were not necessary to support dosing in the comparative clinical study. Therefore, the datasets from the in vivo nonclinical studies will not be submitted for FDA processing, review, and archiving. Does the Agency find this approach to be acceptable?

FDA Response:

We expect study reports for all nonclinical studies (i.e. pdf files) to be submitted with the BLA application. Submission of electronic datasets associated with the in vivo nonclinical studies in Standards for the Exchange of Nonclinical Data (SEND) format is not required at this time.

Discussion:

No discussion took place.

Question 10:
FKB intends to file the BLA with electronic data for all clinical studies excluding FKB327-004, which is a supportive PK comparability study in a Japanese only population. Electronic clinical datasets will be provided according to the CDISC standards such as Study Data Tabulation Model (SDTM) and Analysis Data Module (ADaM). The Applicant believes this format to be acceptable as it is included in the FDA Data Standards Catalog. Validation has been performed using Pinacle21, which includes the vocabulary used. Does the Agency consider this electronic format to be acceptable?

FDA Response:

Your proposed electronic format is acceptable. However, in addition to the electronic clinical datasets, provide all programs and macros used to carry out analyses of key efficacy and safety endpoints. To ensure traceability, provide documentation which clearly details the creation of analysis datasets. Additionally, ensure that all the hyperlinks in the documents work.

Discussion:

No discussion took place.

Question 11:
Executed Batch Production Records are required to be submitted in the BLA. The Applicant plans to submit one executed Batch Production Record from the final PPQ batch. Does the Agency find this approach to be acceptable?

FDA Response:

Your approach is acceptable. Also, see our response to Questions 5.

Discussion:

No discussion took place.

Question 12:
The Applicant plans to request a (b) (4) month expiry period in the BLA for the 20 mg and 40 mg drug product in prefilled syringe and auto-injector presentations. This expiry period will be supported by (b) (4) months real time data on 3 engineering batches. Data from clinical and registration batches ranging from 6 months to 18 months will also be included in the BLA. During the BLA review cycle, updated stability data will be provided on the clinical and registration batches at the 18 and 24 month time points. At the time of expected BLA licensure, (b) (4) month real time stability data will be available for the clinical and registration batches. Does the Agency agree with this approach?

FDA Response:

Yes, we agree with your approach.

Discussion:

No discussion took place.

Question 13:
The Applicant plans to request (b) (4) month expiry period in the BLA for drug substance. This time-period will be supported by (b) (4) months real time data collected on three batches including a toxicology batch, engineering batch and clinical batch. Also, 24-month data from three registration batches used for clinical studies will be included in the BLA. During the BLA review cycle, updated stability data will be provided on the three registration batches at the (b) (4) month time point. At the time of expected BLA licensure, (b) (4)-month real time stability data will be available for the three registration batches. Does the Agency agree with this approach?

FDA Response:

Yes, we agree with your approach.

Discussion:

No discussion took place.

Question 14:
A change in AI components (parts) (b) (4) and a move of manufacture to a new facility (b) (4) will take place at the time of commercialization. Risk assessment and design verification to confirm that the proposed modifications for the AI unit, not directly contacting the DP, have no adverse impact on functionality and product quality will be conducted. The relevant study results will be submitted during BLA review in December 2017. Does FDA find this to be an acceptable approach?

FDA Response:

We do not agree with your proposal to submit additional information during the review cycle. We remind you that your application should be complete at the time of submission, meaning that it must contain all information necessary to support a substantial review of the initial 351(k) BLA. If you are planning to seek approval for the AI presentation in the original 351(k) BLA, all the information necessary to support a regulatory decision about the AI should also be submitted in the original BLA submission. For example, summary data and information demonstrating that (b) (4) does not impact container closure integrity of the pre-filled syringe should be included in the BLA.

If you are unable to submit these data at the time of the original 351(k) BLA submission, you should consider submitting a post-approval supplement for the AI when all the data to support the AI are available, assuming your planned 351(k) BLA is approved.

Also note, facility compliance status will be assessed for the new facility to determine if a pre-approval inspection is needed at the time the information is received in the application/supplement.

FKB Response:

- ***Based on FDA's feedback, FKB will investigate the feasibility for launching the product with the current ('clinical') configuration of the AI without the proposed changes.***
- ***If this can be done, FKB will include full information on the current configuration of the AI in the BLA***
- ***A protocol to assess the comparability of the AI pre- and post-changes will be included in the BLA***
- ***If the comparability protocol is approved and the manufacturing facility is inspected as part of the initial BLA, does FDA agree that the results and conclusions from the comparability study could be reviewed as a CBE-30 post BLA approval?***

Discussion:

The FDA reminded the sponsor that if they plan to pursue licensure of both devices (AI and PFS), the information included in the original BLA submission for both devices should be complete (e.g. PK bridging from the PFS to the AI, device information, human factor studies, actual use studies, etc.). FDA noted that FKB's proposed changes to the AI represent a major manufacturing change. However, the details of these changes and the protocol for assessing the comparability of the pre- and post- change auto-injector were not a part of the meeting package and were not reviewed by the Agency prior to the meeting. The FDA noted that if FKB fails to provide a complete package for either device when submitting the original BLA, it may have implication for the filing determination. In terms of FKB's question on the comparability protocol as a future CBE-30 supplement, the FDA could not comment at the meeting as the focus of discussion was what data are needed for filing of the original BLA submission and not FKB's plans for post-approval submissions. FDA asked if the manufacturing of both AI and PFS will take place at the same facilities. FKB responded that they believe manufacturing of both devices will take place in different facilities at the same location, however they will confirm the facility and location information.

Post-meeting Comment:

Inclusion of a comparability protocol in FKB's original BLA submission is insufficient to support approval of the AI presentation since an inspection of the AI manufacturing facility may

be needed prior to taking a regulatory action. FDA recommends FKB request approval of the AI presentation in a post-approval supplement.

Additionally, a comparability protocol will need to be submitted as a Prior Approval Supplement (PAS). Considering the potential need for an inspection of the manufacturing facility, submitting a comparability protocol will not simplify or accelerate the review process of the AI presentation. FDA recommends FKB to submit all data to support the AI presentation in one PAS.

Question 15:
Manufacturing process optimization of assembling the syringe into the AI - a change in equipment in Terumo Yamaguchi Factory - will take place at the time of commercialization. The proposed optimization is to (b) (4) ***Risk assessment and equipment qualification, including evaluation of functionality, will be conducted to confirm that the proposed modification will have no adverse impact on functionality and there is no need to conduct additional PPQ and/or stability study to investigate the impact on product quality. The relevant study results will be submitted during BLA review in December 2017. Does FDA find this to be an acceptable approach?***

FDA Response:

We do not agree with your proposal to submit additional information during the review cycle. See our response to Question 14 above.

If any batch manufactured using the (b) (4) *assembly is intended for commercial use, information demonstrating that the* (b) (4) *assembly process does not impact container closure integrity of the pre-filled syringe should be included in the BLA.*

FKB's Response:

- ***FKB will include full information on the current*** (b) (4) ***process for the assembly of the AI in the BLA***
- ***A protocol to assess the comparability of the AI pre- and post-changes to the assembly process will be included in the BLA***
- ***If the comparability protocol is approved and the manufacturing facility is inspected as part of the initial BLA, does FDA agree that the results and conclusions from the comparability study could be reviewed as a CBE-30 post BLA approval?***

Discussion:

The FDA was not in agreement with FKB's proposal and referred FKB to the previous discussion under Question 14.

Question 16:
The Applicant plans to conduct shipping validation studies over two seasons, once in summer and twice in winter, for the PFS and AI. Shipping validation during summer will be included in the BLA while the winter data will be provided during BLA review period (May 2017). Does the Agency find this approach to be acceptable?

FDA Response:

Yes, your proposal is acceptable.

Discussion:

No discussion took place.

Question 17:
As discussed within the BPD Type 2 meeting held June 14, 2016, a Human Factors Study is currently underway in pediatric JIA patients. As these study results will not be available prior to BLA filing, they will be provided during BLA review. Nevertheless, due to provision of other Human factors studies, the Applicant considers the BLA to be complete upon filing. Does the Agency agree?

FDA Response:

No, we do not agree with your approach. You propose to submit additional information during the review cycle. See our response to Question 14 above.

FKB's Response:

- ***Human Factors Studies are already complete with data available to support use of FKB327 devices in adult populations and also administration via caregivers and healthcare professionals***
- ***FKB will consider the possibility of submitting the BLA to include the JIA indication only allowing caregiver/HCP administration***
- ***Appropriate provisions will be included in the labelling to ensure no self-administration by pediatric patients***
- ***Does the Agency agree this approach would be acceptable?***

Discussion:

The FDA sought clarification on whether the HF studies for both the AI and PFS presentations were completed. FKB confirmed that HF studies in adults and administration via caregivers and health care professionals for both the AI and PFS presentations were complete. The HF studies for AI and PFS presentations in JIA patients is ongoing.

The FDA noted that excluding the pJIA subjects from self-administrating the drug and only allowing caregiver/HCP administration may be problematic from a clinical and scientific standpoint. The FDA further made a distinction between the expectations for the data necessary to support each of the two presentations. For example, based on a comprehensive use-related risk analysis, the sponsor may determine that a HF validation study is not needed for the PFS and therefore should submit their risk analysis and justification for not conducting the HF validation study to the Agency for review under the IND (see FDA response to Question 25).

The FDA noted, however, that the AI presentation is a new and unique device and in general would require data from one or more HF study(ies), in addition to the drug-device combination product considerations stated in the 2013 Draft Guidance for Industry: Rheumatoid Arthritis: Developing Drug Products for Treatment.[1]

FKB then proposed if FDA would consider not including the pJIA indication in the initial BLA submission. The FDA replied that FKB may seek licensure for fewer indications than those for which the reference product is approved. However, as noted earlier, JIA is the pediatric equivalent of RA, and in seeking licensure for RA, FKB would still need to satisfy the requirements of the Pediatric Research and Equity Act (see "PREA Requirements" below) FDA can provide further feedback in a post-meeting note.

Post-Meeting Comment:

Under PREA you are required to address JIA in your application if you intend to seek licensure for RA. However, for a 351(k) BLA that is otherwise approvable, it could be acceptable, as you have proposed, to seek licensure for the JIA indication and to address the issue of insufficient data to support self-administration by pediatric patients through labeling. This data would be required as part of a PREA post-market requirement.

Question 18:

FKB327 is not the first biosimilar adalimumab to undergo FDA review. The data and information presented in the BLA is not considered to raise additional issues or concerns as compared to the first licensed biosimilar adalimumab (adalimumab-atto, Amjevita™) and the reference product, Humira®. Thus, convening an FDA Advisory Committee to obtain independent advice on the totality of the evidence to support licensure of FKB327 for all the indications for which Humira® is licensed is not anticipated. Does the FDA agree?

FDA Response:

The determination for the need for an Advisory Committee meeting is made after the application has been submitted and a filing decision has been made.

[1] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm354468.pdf

Discussion:

No discussion took place.

Question 19:
The Applicant believes that no additional analytical and functional studies need to be conducted to conclude that FKB327 is highly similar to US-licensed Humira®, notwithstanding minor differences in clinically inactive components. Does the Agency agree?

FDA Response:

We note that the analytical and functional similarity studies were conducted mainly using FKB327 drug substance (DS) lots. In general, analytical similarity analyses should be performed primarily with FKB327 drug product (DP) lots, each individually formulated from a single and unique DS lot, especially for the attributes placed in tier 1 and tier 2 categories. In the analytical similarity assessment in your BLA, all clinical, process validation, and commercial DP lots tested should be included for those attributes evaluated using Tier 1 and 2 statistical methods. In case the number of FKB327 DP lots tested is insufficient to perform a robust statistical analysis, you may include testing results from FKB327 DS lots as long as the DS lots are independent from those used to manufacture the clinical and process validation DP lots. Provide a table listing the genealogy of all DS and DP lots and their usage in your BLA. Also provide an assessment of the impact of DP manufacturing process on the FKB327 quality attributes to justify the use of DS lots of FKB327 in the similarity assessment.

Secondly, as part of the analytical similarity exercise, a forced degradation study that compares the rates and pathways of degradation of FKB327 to those of the reference product should be conducted. You should provide a scientific justification and risk assessment on the stress conditions used in the forced degradation study and the product quality attributes selected for the analysis. Additionally, multiple lots of FKB327 and US-licensed Humira should be included in this assessment to ensure a meaningful comparison.

In addition, you should also include evaluation of the ability of FKB327 and US-licensed Humira to elicit induction of regulatory macrophages in your analytical similarity assessment. Antibody-mediated reverse signaling and induction of regulatory macrophages have been identified in the scientific literature as potential mechanisms of action for anti-TNF monoclonal antibody products [1]. Regulatory macrophages are postulated to play an important role in wound healing and gut homeostasis. In your analytical similarity assessment, you should include a cell-based assay to evaluate induction of regulatory macrophages. A sufficient number of FKB327 lots and the reference product lots should be evaluated to obtain reliable estimates of the activity of both products.

Also refer to additional microbiology comments regarding endotoxin recoverability studies.

FKB's Response:

- ***Thank you for your comments. FKB will take these into consideration when preparing the biosimilarity assessment section.***
- ***FKB agrees with FDA's recommendation to include similarity assessment results of induction of regulatory macrophage.***
- ***This evaluation had not been raised as a requirement for the similarity assessment during recent interactions with FDA (June 2016) . In consideration of the timelines to obtain the results, will FDA accept the provision of these data to potentially be submitted soon after the BLA submission***

Discussion:

The FDA accepted FKB's proposal to submit the assay results evaluating the induction of regulatory macrophages after the original BLA submission; however, FDA requested that prior to submitting the BLA, FKB provide a timeline as to when they plan to submit the assay results and provide a description of the assay methodology. FKB agreed to do so.

Question 20:
A draft Prescribing Information, Instructions for Use, and Medication Guide has been provided. Does FDA consider the format of this labeling to be acceptable? If not, what revisions should be made?

FDA Response:

It would be reasonable to incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications, as a starting point. Submit your draft proposed labeling for FKB327 in Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) formats. We refer you to PLLR formatting for Humira USPI approved on June 30, 2016. We recommend that you also refer to the Draft Guidance for industry: Labeling for Biosimilar Products (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf). We request that your annotated labeling identify, with adequate specificity, the source of all data and information presented. We will provide additional comments on draft proposed labeling during review of your BLA.

[1] Olesen CM, Coskun M, Peyrin-Biroulet L, Nielsen OH. Mechanisms behind Efficacy of Tumor Necrosis Factor Inhibitors in Inflammatory Bowel Diseases. Pharmacology & Therapeutics, 2016; 159:110–119. http://dx.doi.org/10.1016/j.pharmthera.2016.01.001.

Discussion:

No discussion took place.

Question 21:

A Risk Evaluation and Mitigation Strategy (REMS) may consist of a Medication Guide, a patient Package Insert, and/or a communication plan. The FDA may also require certain elements to assure safe use (ETASU) as part of a REMS. The Humira® (BLA 125057) REMS was approved April 2010, where a communication plan to physicians was required to alert and warn healthcare providers about unrecognized histoplasmosis and other invasive fungal infections associated with Tumor Necrosis Factor (TNF) blocker use. In December 2011, the REMS communication plan was demonstrated to have met its goals and hence the REMS was eliminated. The warning is now included in the Prescribing Information and Medication Guide for both Humira® and another biosimilar, Amjevita™. The same warning will be included in the Prescribing Information and Medication Guide for FKB327. Thus, there is no need for a REMS program (such as a communication plan to physicians or ETASU) for FKB327. The Applicant is proposing that the summary of safety concerns for FKB327 is similar to the reference product Humira®. The current risk assessment, taking into consideration important identified risks, potential risks and missing information, indicates that these risks can be identified and mitigated through routine pharmacovigilance and labeling (Prescribing Information and Medication Guide) and this will be described in the contents of Section 1.16.1 Risk Management (non-REMS) for FKB327. Does the Agency agree with this approach?

FDA Response:

In December 2011, FDA released Humira from its previously approved REMS (refer to the letter posted under the approval history for US-licensed Humira at Drugs@FDA with the action date December 13, 2011). The FDA has also determined that "maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21CFR 208.1" (refer to the letter posted under the approval history for US-licensed Humira at Drugs@FDA with the action date July 13, 2011). Accordingly, at this time, developing a Medication Guide for patients would be appropriate for your proposed biosimilar product. Based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS and/or Medication Guide during the review of your application.

Discussion:

No discussion took place.

Question 22:

An Integrated Summary of Immunogenicity (ISI) will be drafted and submitted in the Marketing Authorization Application (MAA) for FKB327 in the EU. This ISI will also be submitted in the BLA. It is intended to fulfill the requirement for the evaluation of immunogenicity on safety and efficacy usually included in the integrated summaries of safety and effectiveness (ISS/ISE). Does FDA agree with this approach?

FDA Response:

Yes, your proposal is reasonable.

Discussion:

No discussion took place.

Question 23:
The Applicant believes that the extent of the clinical data package to be submitted in the BLA filing is sufficient to allow determination from the clinical perspective that FKB327 is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the investigational biosimilar biological product and the reference product in terms of the safety, purity, and potency of the product. Does the Agency agree?

FDA Response:

You propose to submit the clinical data from the completed studies FKB327-001, and FKB327-002. You further propose to submit interim clinical data on patients enrolled in study FKB327-003; specifically, data on almost all patients up to 3 months following the single transition and approximately half of the patients up to 6 months following the single transition (Table 21 from your briefing document). Confirm that these interim data include safety and immunogenicity for each of the treatment arms. Comparative safety and immunogenicity data for a minimum of 6 to 8 weeks following the single transition in study FKB327-003 should be included in the initial BLA submission. The adequacy of the data package to support the BLA will be a review issue.

Discussion:

No discussion took place.

Question 24:
The Applicant is requesting licensure for the following indications: Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Plaque Psoriasis, and Ulcerative Colitis. An ISS and ISE will only be prepared for the patients' studies for the Rheumatoid Arthritis indication. All other indications will be requested via an extrapolation approach. No ISS/ISE for the other indications are planned. In addition, no ISS/ISE for healthy subject studies is planned. Does the Agency find this approach, i.e., only one ISS and one ISE in patients with rheumatoid arthritis, to be acceptable?

FDA Response:

Yes, your approach is reasonable. If FKB327 meets the statutory requirements for licensure as a biosimilar biological product under section 351(k) of the PHS Act based on, among other things, data derived from clinical study(ies) sufficient to demonstrate safety, purity, and potency in an

appropriate condition of use, you may seek licensure of FKB327 for one or more additional conditions of use for which US-licensed Humira is licensed. However, you would need to provide sufficient scientific justification for extrapolating clinical data to support the determination of biosimilarity for each condition of use for which you seek licensure.

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

- *The mechanism(s) of action in each condition of use for which licensure is sought; this may include:*
  - *The target/receptor(s) for each relevant activity/function of the product;*
  - *The binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptor(s);*
  - *The relationships between product structure and target/receptor interactions;*
  - *The location and expression of the target/receptor(s).*
- *The PK and biodistribution of the product in different patient populations (relevant PD measures also may provide important information on the mechanism of action);*
- *The immunogenicity of the product in different patient populations;*
- *Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to "off-target" activities); and*
- *Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population from which licensure is sought.*

The acceptability of your scientific justification based on the mechanism(s) of action of adalimumab and these additional factors listed above for extrapolating data to indications other than rheumatoid arthritis will be a review issue.

Section 351(k)(2)(A)(i)(II) of the PHS Act requires that a 351(k) application for a proposed biosimilar product include information demonstrating that the proposed biosimilar product and the reference product utilize the same mechanism or mechanisms of action for the condition(s) of use for which licensure is sought, but only to the extent that the mechanism(s) of action are known for the reference product. We refer you to the FDA's Guidance for Industry, "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (2015)," which states : "If the clinically relevant mechanism(s) of action are known for the reference product or can reasonably be determined, one or more of the functional assays should reflect these mechanisms of action to the extent possible." Accordingly in your 351(k) BLA submission, provide functional assays, including mechanism(s) of action, comparing your product to the reference product (US-licensed Humira) and include a justification that your product utilizes the same mechanism(s) of action as US-licensed Humira. This data and information should not be limited to the "primary" mechanism of action if other mechanism(s) of action are known or can reasonably be determined. Provide a summary of the data under Module 2.6 ("Nonclinical Written and Tabulated Summaries") and Module 2.3 ("Quality Overall Summary") with a link to the relevant section(s) of Module 3.

Also refer to FDA's response to Question 19.

Discussion:

No discussion took place.

Question 25:

A Human Factors Study is currently underway in pediatric JIA patients. FKB and research partner, (b) (4)., has been actively engaged in recruiting efforts to enroll adolescents diagnosed with JIA, however, the enrollment in the study is delayed due to a particularly small available population of JIA adolescent patients. FKB plans to enroll surrogate indications in the usability evaluations of FKB327 AI and PFS for adolescent patients. The surrogate indications are selected based on research of the physical, cognitive and/or perceptual limitations associated with JIA. Does the Agency agree with this approach?

FDA Response:

No, we do not agree. Your proposed surrogate indications have different clinical manifestations from those of JIA patients. The main consideration for JIA patients who would be using the autoinjector would be of a physical nature (i.e., joint swelling, stiffness, and pain resulting in limited movement of the finger, hand, and wrist joints). Your proposed surrogate conditions would not adequately represent these types of physical limitations as manifested by JIA patients.

We note that you submitted two Human Factors (HF) validation protocols for JIA patients (Appendix 9 for the autoinjector and Appendix 10 for the pre-filled syringe). We remind you that submitting HF validation protocols as part of meeting packages is not the recommended mechanism to seek Agency feedback and we encourage you to submit this information as a separate submission.

However, based on a high level review of your HF validation protocols for the autoinjector and pre-filled syringe in pediatric JIA patients, we have the following recommendations that may help to address the challenges you have faced in recruiting an adequate number of adolescent JIA participants:

1. Regarding your HF study in JIA patients for the pre-filled syringe.

Perform a comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform (consider known problems for similar products), and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

Based on this risk analysis, you will need to determine whether you need to perform a human factors (HF) validation study under simulated use conditions with representative users

performing necessary tasks to demonstrate safe and effective use of the product. The risk analysis can be used to inform the design of a human factors validation study protocol for your product. If you determine that an HF validation study is not needed for your product, submit your risk analysis, samples of your pre-filled syringe, and justification for not conducting the HF validation study to the IND for review. We will notify you if we concur with your determination.

2. Regarding the need for a trained arm in your HF studies:

There are circumstances where it may be acceptable to test untrained users. For example, if it is NOT expected that training will be provided consistently for every intended user in actual use or you have reasonably established that training would not be generally expected to occur with your product, then it may be appropriate for the HF validation study to only test untrained users.

If it is expected that training will be provided consistently for every intended user in actual use, then the training provided in the HF validation study should approximate training that will occur in actual use.

3. Regarding the need for 15 injection experienced participants in your HF studies:

Prior use experience with similar devices is a user characteristic that can impact a user's ability to use a proposed product appropriately. In some cases, there may be negative transfer that can result in use errors/task failures that can lead to harm. We expect that this is examined during formative testing. The results of your formative studies and risk analyses will help guide your decision regarding distinct user groups that should be evaluated in a HF validation study. That said, including a minimum of 15 users that are naïve to the modality and 15 users that have experience is likely to be an acceptable approach for the Agency. However, in consideration of your challenges in recruitment of the JIA patient population and that pediatric/adolescent patients may be less likely to have previous experience with autoinjectors, a total of 15 pediatric JIA participants with a mix of injection naïve and injection experience may be reasonable in this particular circumstance.

We will provide further comments to your Human Factor validation protocols for JIA patients in a subsequent communication after completing our review.

FKB's Response:

- ***FKB strongly believes that a number of the proposed surrogate conditions provide a suitable alternative to JIA in terms of physical impairment***
- ***Use of surrogate indications is supported by the view of FKB's clinical collaborators who indicate that JIA is determined to be the diagnosis for certain adolescents only after several other potential rheumatologic and/or immunologic conditions have been ruled out***
- ***FKB proposes to include within a revised protocol of the HFS an inclusion criterion for physical impairment/limitation that reflects that observed in JIA patients***
- ***With this addition can FDA agree to the use of surrogate patients?***
- ***The revised HF validation protocols for AI and PFS will be provided in a separate submission to obtain Agency feedback***

Discussion:

FKB proposed revising their HF protocol to include surrogate patients with physical impairments and limitations that are similar to those observed in the pJIA population. The FDA replied that with adequate justification, this approach was reasonable. FKB clarified that for the ongoing HF study the "clinical" AI (vs. the fully automated assembly) was used. The FDA also referred the sponsor to the discussion under Question 17 on the expectations for human factor studies for the PFS vs. the AI.

Question 26:
Can the Agency please provide their current thinking on which manufacturing and testing sites for FKB327 will be inspected and the possible time frame for that (these) inspection(s)?

FDA Response:

Manufacturing and testing sites associated with the BLA will be evaluated at the time the application is received to determine compliance status and if an inspection will be conducted.

All manufacturing and testing sites should be ready for inspection when you submit your application. The drug substance manufacturing facility should be in production for FKB327 during the 2-6 month of the BLA review timeframe. The inspection of the drug product facility should occur when the aseptic processing facility is in operation manufacturing the FBK327 drug product or a similar product on the same fill line also within the 2-6 month timeframe.

In addition, submit a table detailing testing site(s) that performed assays to support your analytical similarity assessment. If the testing site(s) is different from the DS or DP manufacturing and QC site, FDA may request separate inspection(s) of these sites during BLA review.

FKB's Response:

- ***FKB will ensure that all manufacturing sites are ready for inspection in line with the FDA comments***
- ***The complete DS manufacturing process takes (b) (4). The manufacturing schedule for FKB327 DS indicates that the manufacture will occur from months (b) (4) after BLA submission. FDA indicated FKB327 DS should be in production 2-6 months after BLA submission. Will this timing allow FDA to determine compliance of the DS manufacturing facility?***
- ***Regarding the inspection of the DP facility, does FDA accept the following manufacturing conditions as a similar product?***

  -Use of similar plastic syringe and process

-Same fill line and equipment

Discussion:

FDA accepted FKB's proposal (outlined on slide 26) regarding the manufacturing conditions for inspection of the DP facility. The FDA advised that FKB ensures the manufacturing and testing sites are ready for inspection when the BLA is submitted, otherwise this may affect FDA's ability to file the application. FDA indicated that FKB may want to adjust the timing of the BLA submission so that DS manufacturing will occur earlier in the BLA review timeframe (2-6 months after the original BLA submission). This will allow adequate time to determine compliance status of the DS manufacturing facility and/or allow adequate time to address any issues that may arise regarding the DS manufacturing process. FDA indicated that a detailed manufacturing schedule for DS and DP manufacturing should be included in the original BLA at the time of submission.

Question 27:
Can the Agency please provide their current thinking on which clinical trials sites for FKB327 will be inspected and the possible time frame for that (those) inspection(s)?

FDA Response:

It will be determined during the filing stage.

Discussion:

No discussion took place.

Additional Questions:

Question 28:

FKB is the Sponsor of the FKB327 IND 116471. As the Sponsor of the IND, FKB initiated and conducted the clinical investigations, preclinical and CMC studies. FKB has responsibility for compliance with FDA regulations for these activities. FKB will be the Applicant of the BLA and this will be documented on the Form FDA 356h.
KKI (Kyowa Kirin Inc.), will be the BLA holder upon licensure. This responsibility will be documented in the BLA cover letter. FKB's responsibilities will change at that time to include regulatory authority correspondence, global quality assurance, global pharmacovigilance, and product development (including the regulatory plan).
KKI will be responsible for final product release, quality assurance for DS and bulk DP, final product supply chain management and pharmacovigilance in the US.
Both FKB and KKI are partially- or wholly-owned subsidiaries of KHK (Kyowa Hakko Kirin Co., Ltd), so they may be considered as 'sister' companies. KHK is the manufacturer of DS in the IND and will also be responsible for DS manufacture for the commercial supplies. KHK will be responsible for release of DS and quality assurance of DS and bulk DP for KKI upon licensure of FKB327.

All responsibilities will be outlined and controlled through agreements. Does FDA find this approach to be acceptable?

FDA Response:

No, we do not agree for the following reasons:

i. *The license holder is expected to establish and apply a robust quality assurance program, and to have knowledge of and control over the manufacturing process for the biological product for which it has a license [2]. Your proposal did not clearly specify which of the three entities will assume complete control of the licensed product.*
ii. *For labeling to comply with 21 CFR610.60(a)(2), and 21 CFR 610.61(b), the licensed manufacturer of the product must appear on the labeling and must be the Applicant shown on form FDA 356h. Your proposed plan to only include the name and address of KHK on the carton label is incompatible with this requirement.*

Therefore, we recommend the BLA applicant and license holder to be a single entity that assumes ultimate responsibility and control on product quality and manufacturing consistency. The license holder can delegate responsibilities upon agreement to the subsidiaries in the product life cycle management.

[2] FDA Guidance on "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product" and FDA Guidance on "Cooperative manufacturing arrangements for licensed biologics".

Discussion:

No discussion took place.

Question 29:

Monosodium glutamate is used in FKB327 Drug Product (DP) as an excipient and complies with the National Formulary (NF). There are several drug products approved in the US which contain monosodium glutamate and are subcutaneously administered. However, maximum amounts of monosodium glutamate in these products to be administered are lower than that of FKB327. Therefore, a safety assessment for the use of monosodium glutamate was conducted based on the information from approved products, and on the information from the non-clinical and clinical studies conducted for FKB327. The result of this assessment supports that the maximum amount of monosodium glutamate in FKB327 to be administered is not considered a toxicological concern. Based on the conformance with NF and the result of the safety assessment, the Applicant believes no additional safety data are needed and that monosodium glutamate is not considered to be a novel excipient. Does the Agency agree with this approach?

FDA Response:

Pending review of your assessment, the monosodium glutamate content in the FKB327 drug product formulation may be acceptable without additional safety evaluation.

Discussion:

No discussion took place.

Additional Nonclinical Comment

Your BLA submission should include a toxicologic safety assessment of leachables derived from the relevant components of the FKB327 container closure system. See USP Chapters <1663> and <1664> for guidance on the assessment of extractables and drug product leachables from pharmaceutical packaging and delivery systems.

Discussion:

No discussion took place.

Additional Combination Product Manufacturing Comments:.

Combination products (see 21 CFR Part 3) are subject to 21 CFR Part 4 "Current Good Manufacturing Practice Requirements for Combination Products" which is accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products . Additional preliminary draft guidance is available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf. As reflected in the final rule on CGMPs for combination products (21 CFR Part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR Parts 210, 211) and with the device quality system (QS) regulation (21 CFR Part 820) through a streamlined approach. If utilizing a streamlined approach, you must demonstrate compliance with either the drug CGMPs or the QS regulation in its entirety and also with those provisions specified in Part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach).

Information to include in BLA Form 356h: List the manufacturing facilities for the combination product and its constituent parts and identify what activities occur at each site (e.g., assembly, filling, sterilization, packaging other) involving which constituents parts (e.g., drug only, device only, both drug and device). For facilities that have manufacturing activities for both drug and device constituent parts, you should identify which CGMP operating system is being used at the

site for the combination product (streamlined or non-streamlined) and if it is a streamlined system, whether it is a drug-CGMP-based or QS-regulation-based system.

Information to include in your application. If you are using a drug-CGMP-based system, you must demonstrate compliance with the following provisions from the QS regulation. Please provide the following information in your marketing application with respect to these requirements. You are not required to provide this information, but we encourage you to do so. Its review will enable the agency to determine whether inspection is needed with respect to these requirements and, if so, to enhance the efficiency of this inspection.

- *Management Responsibility (21 CFR 820.20)*

Provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.

- *Design Control, General (21 CFR 820.30)*

Provide a description of your design control procedures. The procedures must include requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file. Provide a copy or a summary of the plan used to design the combination product. Explain how you utilized the design control process to develop the combination product under review.

- *Purchasing Controls (21 CFR 820.50)*

Provide a summary of the procedure(s) for purchasing controls. The summary should:

a. *Describe your supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.*

b. *Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.*

c. *Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.*

Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

- *Corrective and Preventive Action (21 CFR 820.100)*

Summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. The CAPA system should require:

a. *Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;*

b. *Investigation of nonconformities and their causes;*

c. *Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and*

d. *Verification or validation of the actions taken.*

- *Installation (21 CFR 820.170) and Servicing (21 CFR 820.200)*

If installation and service requirements apply based on the type of device constituent part included in your combination product, the following information should be provided:

Installation. If applicable for the combination product, provide a summary of how your firm has established installation, inspection instructions, and test procedures for the installation of the combination product.

Servicing. Where servicing is a specified requirement for the combination product, provide a summary of how your firm has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements.

Additional 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 BLA submission.

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

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

- *Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).*
- *Microbial data from three successful product intermediate hold time validation runs at manufacturing scale should be provided. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).*
- *Chromatography resin and UF/DF membrane (if applicable) lifetime study protocols and acceptance criteria for bioburden and endotoxin samples to demonstrate adequate microbial control at scale. In addition, provide the bioburden and endotoxin acceptance criteria for resin and membrane storage. Bioburden and endotoxin samples for the storage validation study should be taken at the end of storage prior to sanitization (3.2.S.2.5).*
- *Bioburden and endotoxin data obtained during manufacture of at least three process qualification lots (3.2.S.2.5).*
- *Information and summary results from the shipping validation studies (3.2.S.2.5).*
- *Drug substance bioburden and endotoxin release specifications (3.2.S.4).*
- *Summary report and results from bioburden and endotoxin test methods qualification performed for in-process intermediates and the drug substance (3.2.S.4).*

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

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

- *Identification of the manufacturing areas and fill line, including area classifications.*
- *Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.).*
- *Sterilizing filtration parameters.*
- *The wetting agent used for post-use integrity testing of the sterilizing filter and the acceptance criterion for passing post-use integrity testing.*
- *Parameters for filling, stoppering, and capping.*

- *Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.*
- *Processing/hold time limits, including the time limit for filtration.*
- *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.*

Include the following study protocols and validation data summaries included in Section 3.2.P.3.5:

- *Bacterial filter retention study for the sterilizing filter.*
- *Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program. For information located in Drug Master Files (DMFs), provide Letters of Authorization which list the relevant depyrogenation and sterilization sites and which clearly identify the location of the relevant information within the DMF.*
- *In-process microbial controls and hold times. Three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.*
- *Isolator decontamination, if applicable.*
- *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.*
- *Shipping validation studies, including container closure integrity data. Additionally for PFS, the difference in air pressures during air shipment may cause movement of the plunger which may breach the sterility of PFS. Include results to demonstrate that the PFS plunger movement during air transportation does not impact product sterility.*
- *Data to demonstrate that assembly into the autoinjector does not impact container closure integrity of the prefilled syringe.*

Provide the following method validation information:

- *Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Information demonstrating the maintenance of container closure integrity after the assembly of the 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 at the initial time point and every 12 months (annually) until expiry.

- *Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.*
- *Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21CFR610.13 (b).*
- *Certain formulations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of standard endotoxin (CSE or RSE) into undiluted drug product and then testing for recoverable endotoxin over time.*

Discussion:

No discussion took place.

Additional Discussion at the end of the meeting:

- FKB asked for a status update on FDA's response to the amendment submitted on October 17, 2016. FDA stated that comments will be forthcoming within the next few months.

Post-Meeting Comment:

The FDA issued the comments to the Sponsor on February 10, 2017.

- FKB sought guidance on the number of suffixes for the non-proprietary name. The FDA responded that the average number is 3 to 6 suffixes and that the proposed suffixes may be submitted to the IND for review and/or ready for submission to the original BLA.

Post-meeting Comment:

Please note that the provisions of this guidance that describes the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 ("PRA").

- FKB inquired about the location for providing the justification for extrapolation and if Module 2.5 would be an acceptable location. The FDA agreed.
- FKB confirmed that safety and immunogenicity data from study FKB327-003 will be submitted to the original BLA, as outlined in Table 21 in the briefing material.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

PRESCRIBING INFORMATION

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

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

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

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

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

1. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

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

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

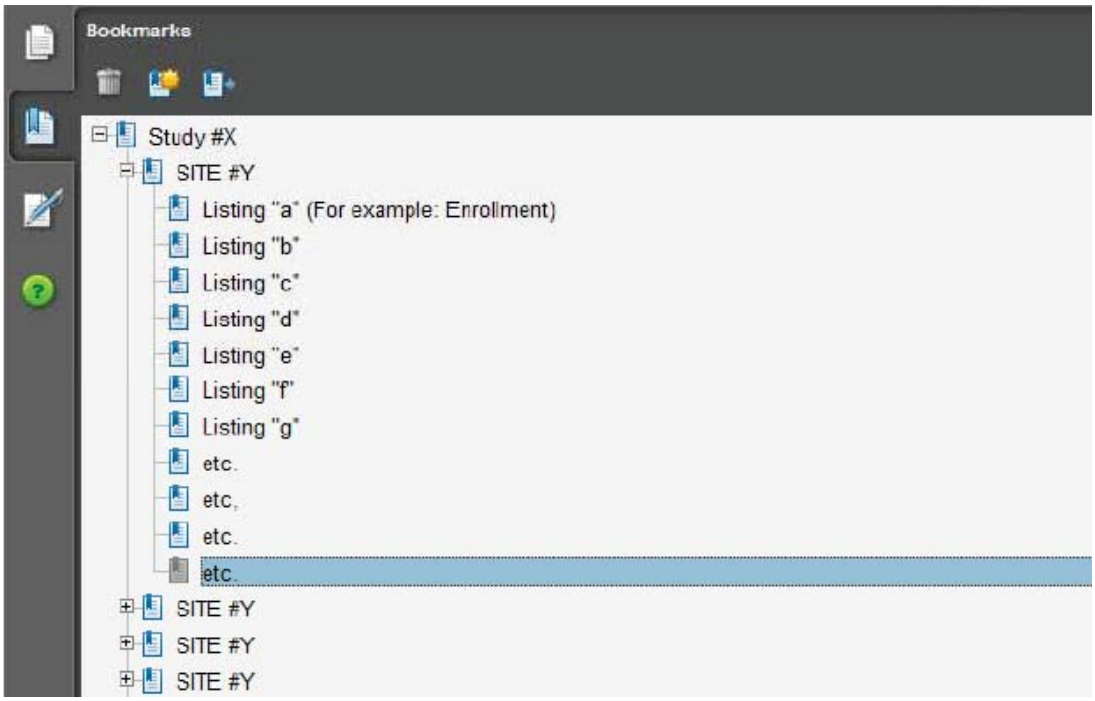
maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

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

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[2]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[2] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

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

For general help with eCTD submissions: ESUB@fda.hhs.gov

PREA REQUIREMENTS

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

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

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

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP. The initial PSP must include an outline of the pediatric study or studies that a sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); and any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive initial PSP that addresses each indication. For indications for which the labeling for the reference product contains adequate pediatric information, you may be able to fulfill PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to your proposed product (see question and answer I.11 in FDA's guidance for industry on

Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009). For conditions of use for which the reference product does not have adequate pediatric information in its labeling, a waiver (full or partial), or a deferral, may be appropriate if certain criteria are met.

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

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are

accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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 and the CDER/CBER Position on Use of SI Units for Lab Tests website found at
http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

FKB's slide deck

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

/s/

SADAF NABAVIAN
04/14/2017